2015•2016
FACULTEIT INDUSTRIËLE INGENIEURSWETENSCHAPPEN
master in de industriële wetenschappen: chemie

Masterproef

Development of the first Suzuki-Miyaura cross-coupling for the formation of alkylfluorostilbenes and studies of the *E/Z*- isomerization of (2-bromo-2-fluorovinyl) benzene derivatives

Promotor :
dr. Rita DE WAELE

Promotor :
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Yordi Stelten

Scriptie ingediend tot het behalen van de graad van master in de industriële wetenschappen: chemie

Gezamenlijke opleiding Universiteit Hasselt en KU Leuven

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Figure 1: A picture of the MSAP-team on 25 may 2016.

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NOMENCLATURE

ABBREVIATION	DESCRIPTION
$BuB(OH)_2$	Butylboronic acid
Conv.	Conversion
DCM	Dichloromethane
dppe	1,2-Bis(diphenylphosphino)ethane
dppf	1,1'-Ferrocenediyl-bis(diphenylphosphine)
Ir-based-photosensitizer	[4,4'-Bis(1,1-dimethylethyl)-2,2'-bipyridine-N1,N1']bis[5-difluoro-2-[5-(trifluoromethyl)-2-pyridinyl-N]phenyl-C]Iridium(III) hexafluorophosphate or $[Ir\{dF(CF_3)ppy\}_2(dtbpy)]PF_6$
PPh_3 or PCy_3	Tricyclohexylphosphine
$Pd(dppf)Cl_2 \cdot DCM$	[1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane
$Pd_2(dba)_2$	Tris(dibenzylideneacetone)dipalladium(0)
PPh_3	Triphenylphosphine
RT	Room temperature
$Ru(bpy)Cl_2$	Tris(2,2'-bipyridyl)dichlororuthenium(II) hexahydrate
SM	Starting Material of a reaction. Usually referred to the starting material for the Suzuki-Miyaura cross-coupling.
TFP	Tri(2-furyl)phosphine
THF	Tetrahydrofuran
tol.	Toluene
Xantphos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene
Xphos	2-Dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl

ENGLISH ABSTRACT

Development of new methodologies for the synthesis of fluoro-organic compounds have gained great interest during the past decades, especially for applications in the fields of medical chemistry and agro chemistry. Introduction of fluorine atoms can substantially enhance biological properties such as bioavailability, lipophilicity, half-time and absorption.

The aim of this master's thesis is to develop the first Suzuki-Miyaura cross-coupling reaction leading to alkylfluorostilbenes in collaboration with the MSAP-team. Different reaction parameters like temperature or the nature of the catalyst have been investigated and the scope of the reaction has been identified. Secondly, the (*E*/*Z*) photo-isomerization of (*E*/*Z*)-(2-bromo-2-fluorovinyl)-benzene derivatives was studied. Different photosensitizers under UV irradiation (365 nm) were tested in order to enrich the mixture with only one isomer. Subsequently, effect of the solvent, temperature and substituents of the phenyl ring on the isomerization ratio and rate were investigated.

The first Suzuki-Miyaura cross-coupling reaction with (*E*/*Z*)-(2-bromo-2-fluorovinyl)-benzene derivatives and alkylboronic acids as coupling partners was developed with yields above 80% and maintaining excellent stereoselectivity. Regarding the isomerization reaction, 2 photosensitizers (benzil and 9-fluorenone) show promising results and further studies are still ongoing in the laboratory to obtain a robust protocol.

DUTCH ABSTRACT

De ontwikkeling van nieuwe synthesemethodes voor fluor bevattende organische verbindingen kende in de afgelopen decennia een enorme toename, vooral in de farmaceutische en de agrochemische sector. De introductie van fluoratomen kan de biologische eigenschappen van verbindingen verbeteren, zoals de biobeschikbaarheid, vetoplosbaarheid, verblijftijd in het lichaam en absorptie.

Het doel van deze masterproef is de ontwikkeling van de eerste *Suzuki-Miyaura cross-coupling* reactie voor de synthese van alkylflourstilbenen in samenwerking met de MSAP groep. Verschillende reactieparameters zoals temperatuur en aard van de katalysator werden onderzocht en de mogelijkheden van de reactie werden bestudeerd. Verder werd de door licht geïnduceerde (*E*/*Z*) isomerisatie van (2-broom-2-fluorvinyl)-benzeenderivaten bestudeerd. Verschillende *photosensitizers* werden bestudeerd onder UV bestraling (365 nm) met als doel een isomeer aan te rijken. Hierna werd het effect van het solvent, de temperatuur en de substituenten op de aromatische ring op de isomerisatiereactie bestudeerd.

De eerste Suzuki-Miyaura reactie voor de koppeling van (2-broom-2-fluorvinyl)-benzeenderivaten aan alkylboorzuren werd ontwikkeld met rendementen hoger dan 80% en uitstekend behoud van de stereochemie. Twee *photosensitizers* (benzil en 9-fluorenon) gaven veelbelovende resultaten in de isomerisatiereacties. Verdere studies in het labo moeten de robuustheid van het protocol verhogen.

1 INTRODUCTION

1.1 Presentation of the Research Group MSAP

This master's thesis and internship take place at the research group 'Miniaturisation pour la Synthèse, l'Analyse, et la Protéomique' (MSAP, USR CNRS 3290) from the University of Lille 1. The MSAP works on service and research in chemistry and biology.

MSAP consists of three components (Figure 2). The first component is a Proteomics platform supervised by dr Christian Rolando and Caroline Tokarski (MCF). The second and third component are dedicated to research. The component 'Development' focuses on analytical development and is also supervised by Christian Rolando. and Caroline Tokarski. The third component, 'Flow Chemistry', is supervised by Maël Penhoat (MCF).

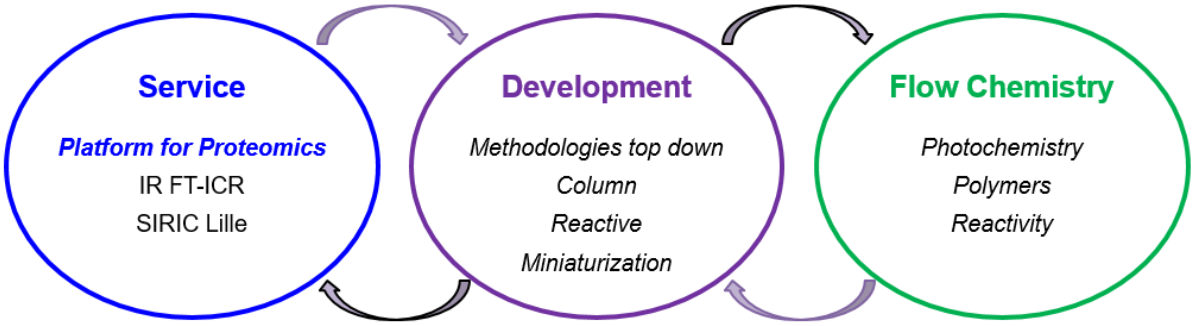


Figure 2: the structure of MSAP

The structure of MSAP is organized in a non-hierarchical way. Every researcher works on one main research subject. The variety in research fields allows collaborations with the majority of the units of the institute Michel Chevreul and FRABio FR3688.

The research conducted for this master thesis is part of the 'Flow Chemistry'-component. It covers organic reactivity and photochemistry.

1.2 Importance of fluorine containing substances

Fluoro chemistry has gained a significant importance in a wide variety of research fields. The development of new fluorine methodology is particularly important for pharmaceuticals and agrochemicals. For example, selective fluorination can provide new drugs with an increase of pharmaceutical effectiveness, biological half-life and bioabsorption. Hence, the current top-selling pharmaceuticals all contain fluorine atoms. Furthermore, fluorine compounds contribute to the development of photovoltaic solar cells and to the positron emission tomography (PET) techniques. Fluorine has a high sensitivity in nuclear magnetic resonance (fluorine-19 NMR), which is interesting for biological studies [1].

As an example of the strength of fluorinated components, the structure of Vinorelbine (Navelbine®, Figure 3) is introduced. This substance belongs to the class of Vinca Alkaloids, which means that it can be derived from the Vinca-plant, 'Madagascar Rosy Periwinkle' [2]. Vinorelbine is commonly used in chemotherapy for the treatment of Non-Small Cell Lung Cancer (NSCLC).

Fluorine atoms can be introduced into Vinorelbine through a di-fluorination reaction [3] to create the structure of Vinflunine (Figure 4). This pharmaceutical, developed by Pierre Potier and his colleagues from CNRS in France, is used for the treatment of lung cancer and metastatic breast cancer [4].

The presence of the difluoride in Vinflunine provides an anti-tumour activity superior to the substance without the fluorine component. The increase of effectiveness was not rationalized so far [3].

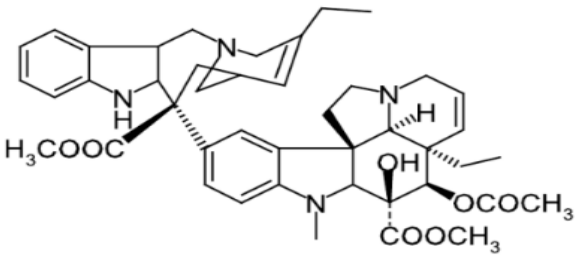


Figure 3: The chemical structure of Vinorelbine [3].

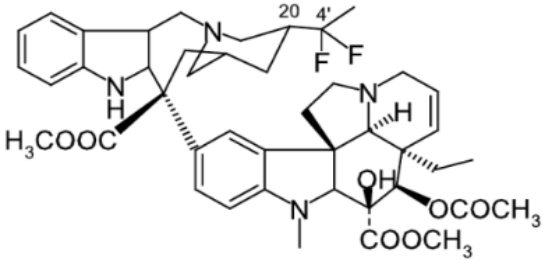
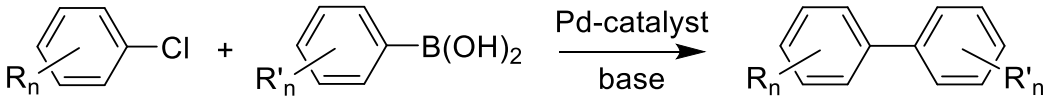


Figure 4: The chemical structure of Vinflunine [3].

1.3 Suzuki-Miyaura coupling reaction

In this research an original methodology to obtain fluorinated compounds based on the Suzuki-Miyaura cross-coupling reaction will be developed. This coupling is one of the most important metal-catalysed reactions for both academics and industrials [5]. This reaction was first published in 1979 by Akira Suzuki. In 2010, the Chemistry Nobel Prize was won by R.F. Heck, E. Neighs, and A. Suzuki for palladium catalysed cross-coupling reactions [6]. The Suzuki-Miyaura reaction that leads to the formation of new carbon-carbon bonds from boronic acid and halide as coupling partners is shown in Reaction 1.



Reaction 1: General concept of the original Suzuki-Miyaura reaction [5].

In this research, a new methodology based on the Suzuki-Miyaura reaction will be developed to obtain alkylfluorostilbenes (Figure 5). In this structure an aliphatic group (-R) is located at the β-place from the aromatic group. On the same carbonic atom, a fluorine atom is located. Fluorostilbenes are an important class of compounds that have anti-carcinogenic, anti-oestrogenic and enzyme inhibitor properties [7].

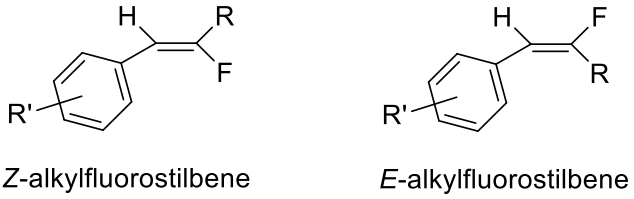


Figure 5: General structure of alkylfluorostilbenes (R=aliphatic).

1.4 *E/Z* stereo isomerism

As shown in Figure 5, alkylfluorostilbenes can appear as two different isomers due to the presence of the double bound. *E-Z* describes the absolute stereochemistry of the double bond. The isomers can have very different physical and chemical properties [8].

In IUPAC nomenclature, this phenomenon is referred to by 'cis-trans' or '*E-Z*'. For compounds that only consist of carbon and hydrogen around the unsaturated bond, 'cis-trans' can be used. Other structures use '*E-Z*', in which case the Cahn-Ingold-Prelog (CIP) priority rules can be used to determine the *E* and *Z* form of the compound. The CIP basically uses the molecular weight of the atoms directly next to the unsaturated carbon to determine the priority of the groups. The atom with the highest molecular weight receives the highest priority [9] (see Figure 6). If the higher priority groups are directly on opposite sides of the double bond, an '*E-*' is added in front of the name. '*Z-*' is added if the groups are on the same side of the bond.

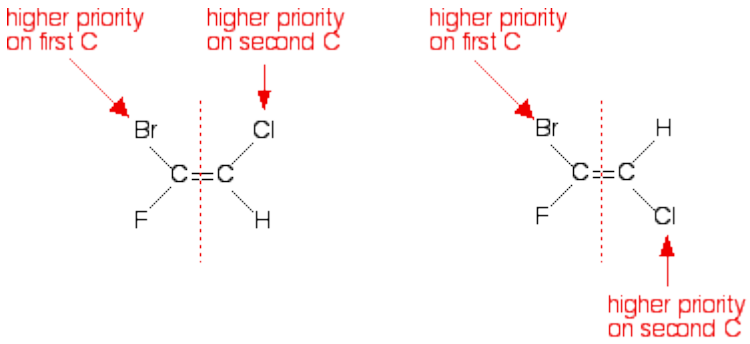


Figure 6: Examples of the Z-isomer (left) and the E-isomer [9].

When the CIP priority rules are applied and the stereochemistry compared before and after the Suzuki-Miyaura reaction, it seems like the *E-Z* form inverses. This is due to the loss of bromine during the reaction. In the starting material, bromine has the priority over fluorine (Figure 7). In the coupled product, fluorine has the priority over the carbon of the butyl-group.

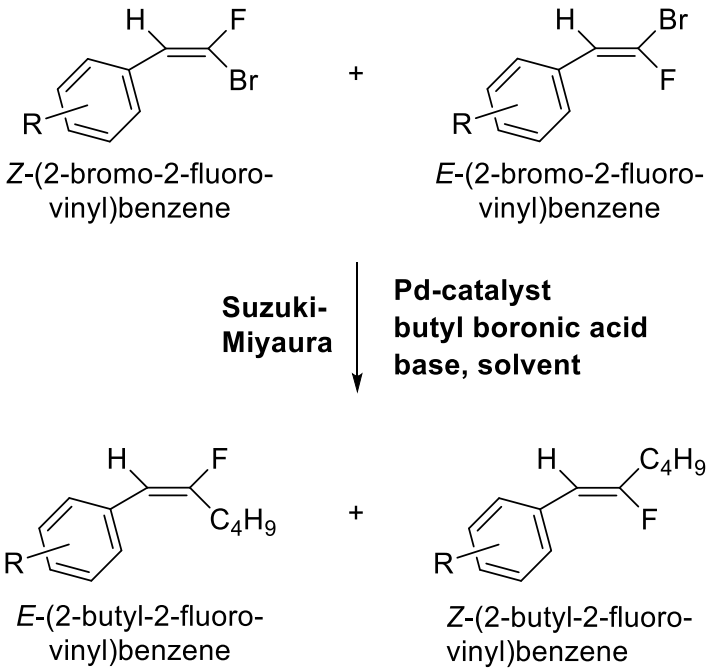
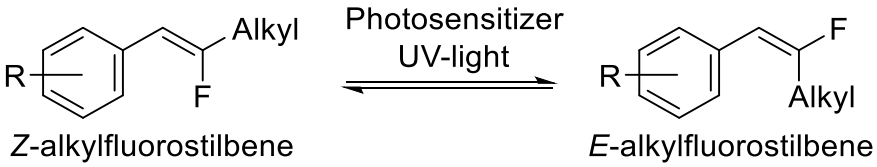


Figure 7: The change of absolute stereochemistry during the Suzuki-Miyaura reaction on fluorostilbenes.

1.5 Isomerization

The products of the Suzuki-Miyaura reaction are most likely formed in a mixture of both *E*- and *Z*-isomers (paragraph 1.4). As only one of the products is usually desired, the other needs to be converted to the desired form. This process is called isomerization.

One way to achieve this isomerization is via the use of a photosensitizer and UV-light radiation (Reaction 2). The mechanism is based on a photo induced isomerization [10]. Theoretically, an energy barrier needs to be overpassed to perform the reaction. Depending on the form (*E* or *Z*), this barrier may vary [11]. Since the *E*-isomer is the thermodynamic product (more stable), the isomerization from *Z* to *E* is more commonly described in the literature [12]. As a result, we expect the isomerization of the *E*-isomer to the *Z*-isomer to be harder to perform.



Reaction 2: Isomerization with the aid of a Photosensitizer and UV-light.

More information about the known methods to obtain only one single isomer is given in paragraph 2.4.2.

1.6 Flow chemistry

Since flow chemistry is a relatively new branch of chemistry, it might be necessary to introduce this subject.

With flow chemistry, chemical reactions are performed in a pipe or tube. The reagents can be pumped through the system with pumps and mixed in a mixing unit [13]. Flow reactors are available in many forms, from simple tubes or double layered tubes to systems with separate cooling channels. Reactors can be fabricated with different materials like plastics and glass.

The major advantages of flow chemistry are faster and safer reactions, better temperature control and quick reaction optimization [13]. The high surface area to volume ratio allows better heat and mass transfer. Cooling and heating can be obtained almost immediately. The small quantities and the fast cleanability of reactors can provide a fast variation of chemical reactions. Flow chemistry can also pose a different approach for reactions that are impossible to perform in batch processes due to the toxic, instability or short lifetime of some chemicals. Extreme temperatures can be easier controlled in flow chemistry. Another advantage is the possibility of in line process control with LCMS or FTIR systems. The overall selectivity or yield of a reaction can be improved compared to batch, since the reaction conditions are perfectly controlled under flow conditions [14].

In practice, the residence time can be adapted by adjusting the flow rate of the liquid. This can be obtained with high sensitive pumping systems:

$$flow\ rate\ (ml/min) = \frac{volume\ of\ the\ reactor\ channels\ (ml)}{desired\ residence\ time\ (min)}$$

2 LITERATURE REVIEW

This literature review is a brief summary of a few aspects of the Suzuki-Miyaura reaction. The mechanism and side reactions are discussed, as well as previous research on this subject. This will give a fundamental basis to the problem definition and objectives (paragraph 3).

2.1 Mechanism of the Suzuki-Miyaura cross-coupling reaction

Figure 8 shows the mechanism of the Suzuki-Miyaura reaction. Hereby is L_n the ligand of the palladium catalyst. This study of the mechanism is important to understand the influence of the reactants (catalyst, ligand, solvents and base) that are used during the reaction.

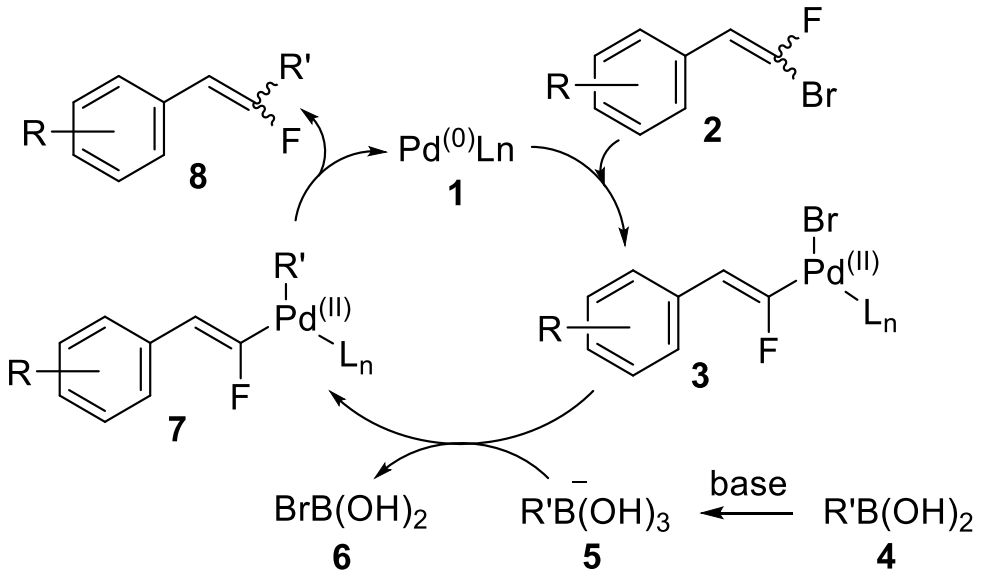


Figure 8: Mechanism of the Suzuki-Miyaura reaction for alkylfluorostilbenes [2] [5].

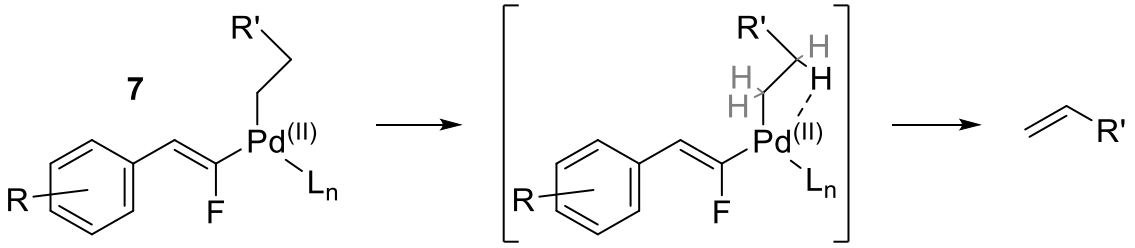
In the first step, component **2** will react with the palladium catalyst **1** through an *oxidative addition*. According to Kavola [5], the base used can influence the formation of the product **3**. To facilitate the *transmetalation,* a more reactive organopalladium alkoxide (R-Pd-OR) or an organopalladium hydroxide (R-Pd-OH) is formed. The *oxidative addition* is often the rate determining step of the catalytic cycle. The catalyst, ligand and the base used have an important influence, in particular the ligand [5].

The second step, called the *transmetalation*, turns form **3** into **7**. In order to allow this step, the alkylboronic acid (**4**) needs to be activated by a base [5]. The *transmetalation* can be influenced by the solvent, the base and the ligand of the palladium catalyst.

In the third and final step of the cycle, the palladium catalyst is regenerated to his original form **1**. The desired product **8** (alkylfluorostilbene) is formed through a *reductive elimination*. This step does not change the stereochemistry of the product [5]. The solvent and the ligand of the catalyst influence this step of the cycle.

2.2 β-hydrogen elimination

A side product can also be formed during the course of the reaction through a β-H elimination pathway. A hydrogen atom, located at the β-position from the palladium atom, can perform an undesired elimination reaction (Reaction 3).



Reaction 3: the β-hydrogen elimination at the organopalladium compound [15].

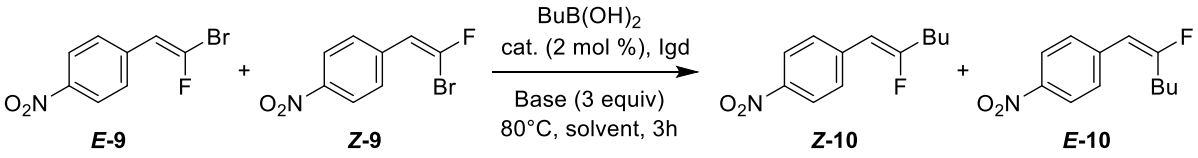
The β-hydrogen elimination can only take place when the hydrogen can approach close enough to the palladium to form a four member palladocycle intermediate in a coplanar conformation [16]. Another condition for the β-hydrogen elimination is the presence of an unsaturated carbon string.

The original Suzuki-Miyaura reaction (Reaction 1) was performed with aromatic halides as coupling partners, where the β-hydrogen elimination pathway is not possible. Because of the aliphatic nature of one of the coupling partners in this study, this unwanted elimination reaction can be envisaged, which adds an extra difficulty.

The presence of a bulky electron-rich ligand can prevent this elimination when it is used with the palladium catalyst. Changing the solvent could possibly aid too. Lastly, it has been demonstrated that the use of a nickel-based catalyst instead of a palladium-based, supresses the elimination reaction [16]. This last solution is excluded since only palladium catalysts are considered in this research.

2.3 Previous Research performed at MSAP: optimization by Laetitia Chausset-Boissarie

The external promotor of this study, dr. Laetitia Chausset-Boissarie, has already performed some experiments on the Suzuki-Miyaura cross-coupling reaction. She has set a fundamental basis for further research by performing 'Reaction 4' on fluorostilbenes and butylboronic acid.



Reaction 4: the Suzuki-Miyaura reaction between fluorostilbenes and butylboronic acid [17].

Laetitia Chausset-Boissarie has tested 5 palladium catalysts, 8 ligands, 5 bases and 4 solvents in her optimization. Each of these products play a different role in the mechanism of the Suzuki-Miyaura reaction (See section 2.1). The selectivity of the reaction and the yield were optimized and results are described in Table 1.

Table 1: Summary of the research performed by Laetitia Chausset-Boissarie on the Suzuki-Miyaura reaction

entry	*E*/*Z*-9	catalyst	ligand	base	Solvent[a]	*Z*/*E*-10	yield[b]
1	55:45	$Pd(Ph_3)_4$	-	Cs_2CO_3	Toluene/H_2O	-	-
2	55:46	$Pd_2dba_3.CHCl_3$	-	Cs_2CO_3	Toluene/H_2O	-	-
3	46:54	$Pd_2dba_3.CHCl_3$	PPh_3	Cs_2CO_3	Toluene/H_2O	-	-
4	46:54	$Pd_2dba_3.CHCl_3$	dppe	Cs_2CO_3	Toluene/H_2O	48:52	41
5	46:54	$Pd_2dba_3.CHCl_3$	Xantphos[c]	Cs_2CO_3	Toluene/H_2O	49:51	86
6	46:54	$Pd_2dba_3.CHCl_3$	Xphos[d]	Cs_2CO_3	Toluene/H_2O	60:40	35
7	46:54	$Pd_2dba_3.CHCl_3$	TFP[e]	Cs_2CO_3	Toluene/H_2O	42:58	78
8	49:51	$Pd_2dba_3.CHCl_3$	$(CH_3OC_6H_4)_3P$	Cs_2CO_3	Toluene/H_2O	54:46	42
9	39:61	$Pd_2dba_3.CHCl_3$	PPh_3	Cs_2CO_3	Toluene/H_2O	52:48	21
10	55:45	$Pd_2dba_3.CHCl_3$	dppf	Cs_2CO_3	Toluene/H_2O	51:49	91
11	44:58	$Pd(OAc)_2$	dppf	Cs_2CO_3	Toluene/H_2O	78:27	37
12	44:58	$PdCl_2$	dppf	Cs_2CO_3	Toluene/H_2O	-	-
13	55:45	$PdCl_2$dppf	-	Cs_2CO_3	Toluene/H_2O	55:45	97[f]
14	55:45	$PdCl_2$dppf	-	K_2CO_3	Toluene/H_2O	46:54	76
15	55:46	$PdCl_2$dppf	-	Na_2CO_3	Toluene/H_2O	57:43	44
16	55:45	$PdCl_2$dppf	-	K_3PO_4	Toluene/H_2O	51:49	93
17	55:46	$PdCl_2$dppf	-	$Ba(OH)_2$	Toluene/H_2O	-	-
18	39:61	$PdCl_2$dppf	-	Cs_2CO_3	Toluene	38:62	95
19	39:61	$PdCl_2$dppf	-	Cs_2CO_3	Dioxane	SM[g]	-
20	39:61	$PdCl_2$dppf	-	Cs_2CO_3	THF	SM[g]	-

[a] The volume ratio of Toluene/H_2O was 10/1. [b] *E*/*Z*-1 (0.12 mmol) and 2a (0.146 mmol) were used; yield was determined by 1H NMR using trimethoxybenzene as interne standard. [c] 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene. [d] 2-Dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl. [e] Tris(2-furanyl)phosphine. [f] the reaction time was 30min. [g] Only the starting material (SM) was found after the reaction.
[17, p. 1]

The catalysts that have proven to give the best yields are $Pd_2dba_3.CHCl_3$ in combination with the ligand Xantphos and catalyst $PdCl_2dppf$. Further studies will be done to demonstrate the generality of the catalystic system. The best base for the reaction is Cs_2CO_3. As for the solvents, toluene/H_2O in a volume ratio of 10/1 proves to be the best solvent. The use of the solvent toluene (without water) gives a good yield, but the reaction is not stereospecific. The reaction doesn't work in dioxane and tetrahydrofuran.

2.4 Related research, not performed at MSAP

With every project it is important to look at previous researches in order to get a better understanding of the subject and to know where there is still room for improvement. This part of the literature study describes related methodologies.

2.4.1 Synthesis of 1-fluoro-1-bromo-alkenes

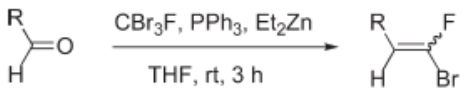
1-fluoro-1-bromo-alkene was obtained through a Wittig reaction involving an aldehyde and bromofluoromethylene ylide (Ph_3P=CBrF) (Table 2). Depending on the substrate, the yield of the reaction varies. Slight variations in *Z*/*E*-ratio are obtained through this reaction [18].

Table 2: Synthesis of bromofluoroalkenes [18], [19].

substrate	PR_3	carbene source	base or metal	solvent	temp. (°C)	product	yield (%)	*Z*/*E*
PhCHO	PPh_3	CBr_3F	--	triglyme	70	PhCH=CBrF	64	54:46
PhCHO	PPh_3	$Ph_3P(Br)CBr_2F$	--	THF	70	PhCH=CBrF	70	55:45
PhCHO	--	$Ph_3P(Br)CBr_2F$	Zn	triglyme	rt	PhCH=CBrF	64	55:45
$PhC(O)CH_3$	PPh_3	CBr_3F	--	triglyme	70	$PhC(CH_3)$=CBrF	18	53:47
$PhC(O)CH_3$	PPh_3	$Ph_3P(Br)CBr_2F$	--	THF	70	$PhC(CH_3)$=CBrF	45	46:54
$PhC(O)CH_3$	--	$Ph_3P(Br)CBr_2F$	Zn	triglyme	rt	$PhC(CH_3)$=CBrF	55	51:49
$PhC(O)CF_3$	PPh_3	CBr_3F	--	CH_3CN	rt	$PhC(CF_3)$=CBrF	92	58:42
$PhC(O)CF_3$	PPh_3	$Ph_3P(Br)CBr_2F$	--	CH_3CN	rt	$PhC(CF_3)$=CBrF	97	56:44
$PhC(O)CF_3$	--	$Ph_3P(Br)CBr_2F$	Zn	triglyme	rt	$PhC(CF_3)$=CBrF	86	52:48

Secondly, a modified Wittig reaction [20] uses diethylzinc (Et_2Zn) in combination with PPh_3 and CBr_3F to generate the ylide intermediate to synthesize 1-fluoro-1-bromo-alkenes (Table 3). The reaction generated good yields and stereoselectivity.

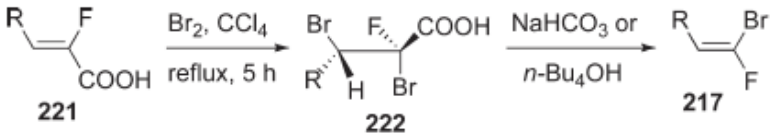
Table 3: Scope of the Wittig reaction developed by Pannecoucke and co-workers [19], [20].



R[a]	yield (%)	*E*/*Z*
$PhCH_2CH_2$	88	1/1.05
$TBDPSOCH_2CH_2$	90	1/0.88
$4\text{-}O_2NC_6H_4$	85	1/0.73
$4\text{-}MeOC_6H_4$	94	1/1.03
$4\text{-}FC_6H_4$	73	1/0.96

A third possible way to synthesize 1-fluoro-1-bromo-alkenes is by addition of bromide to an alkene, followed by an elimination [21], [22]. The reaction is stereoselective since only the *Z*-isomer is formed. However, in case of **221b** and **221j**, the bromination wasn't selective, thus a *Z*/*E*-mixture was synthesized (Table 4).

Table 4: Bromination and elimination reaction developed by Eddarir and co-workers [19], [21], [22].

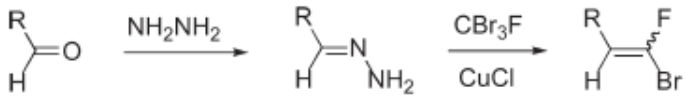


	R	**222** yield (%)	**217** yield (%)
b	$MeOC_6H_4$	93	70[a]
g	Ph	84	82
h	$4\text{-}ClC_6H_4$	88	59
i	$4\text{-}O_2NC_6H_4$	82	83
j	$n\text{-}C_5H_{11}$	72	60[b]

[a]*Z*/*E* = 63/27, [b]*Z*/*E* = 86/14

Finally, the product could be obtained via a hydrazine intermediate generated from an aldehyde by addition of CBr_3F in presence of CuCl (Table 5) with good yield and low stereoselectivity [23]. The reaction is compatible with electron donating and withdrawing groups.

Table 5: Synthesis of 1-Fluoro-1-Bromoalkenes developed by Shastin and co-workers [19], [23].



R[a]	yield (%)	*E*/*Z*
$4\text{-}NO_2C_6H_4$	87	3.5:1
$2\text{-}NO_2C_6H_4$	86	3.3:1
$4\text{-}ClC_6H_4$	86	6:1
2-Py	95	1.8:1
$2,6\text{-}Cl_2C_6H_3$	48	21:1

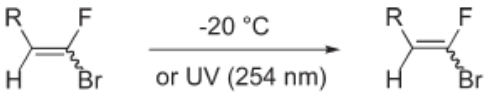
[a]Only representative examples are reported.

2.4.2 Methods to obtain a pure E- or Z- isomer of bromofluoro-1-alkenes

The separation of the 2 isomers are not possible via usual purification techniques like column chromatography or distillation. Giorgio [19] described a series of methodologies to obtain a single isomer, apart from the isomerization with UV-light and a photosensitizer (paragraph 1.5).

Firstly, a catalytic amount of bromine can provide an almost clean *E*-isomer (*E*/*Z*-rate of 92:8) of 1-bromo-1-fluoro-2-phenylethylethylene. However with low yield [7] [24]. Presumably, catalytic amounts of bromine could even cause an isomerization of bromofluoroalkenes when stored at -20 °C for one week (Table 6). The *E*/*Z*-rate changed from about 50:50 to *E*/*Z*-rates of at least 75: 25. The same research-group achieved an isomerization by photolysis at 254 nm which also formed *E*/*Z*-ratios above 75:25.

Table 6: Isomerization with the aid of bromine or UV-light [7], [19], [24].

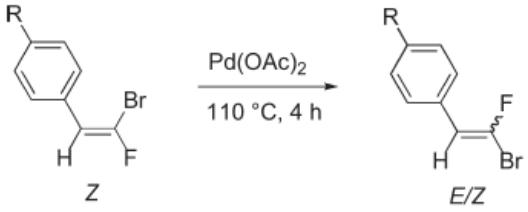


R	*E/Z* starting alkene	yield (%) (*E/Z*) product
Ph	44:56	77 (82:18)
2-ClC_6H_4	48:52	67 (82:18)
4-$MeOC_6H_4$	66:34	62 (81:19)[a]
4-FC_6H_4	72:28	45 (87:13)
3-$O_2NC_6H_4$	63:37	53 (76:24)
1-naphthyl	49:51	46 (49:51)
PhCH(Me)	42:58	52 42:58)
n-C_7H_{15}	46:54	72 (46:54)

[a]Photolysis gave an *E/Z* ratio of 78:22

Secondly, a metal-catalysed isomerization was developed (Table 7). $Pd(OAc)_2$ is described as a possible catalyst for the reaction [22]. However, the results of this isomerization are only partially successful, as the substituent on the aromatic ring seems to have a big impact on the *E*/*Z*-ratio.

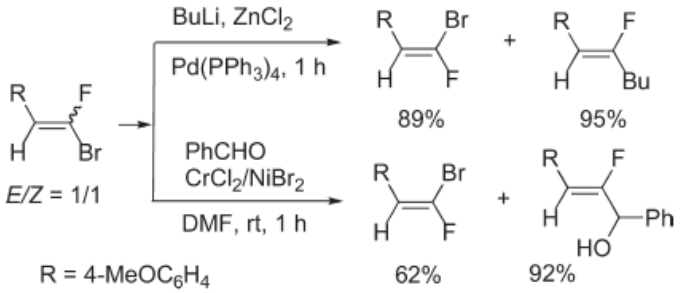
Table 7: Metal-catalysed isomerization [19], [22].



R	*E/Z*	R	*E/Z*
H	89:11	OMe	50:50
Cl	88:12		

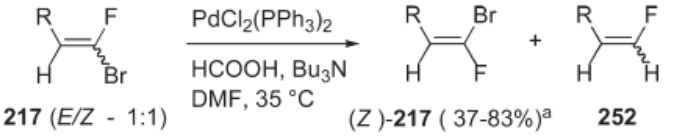
Thirdly, exploiting the different reactivity between the two isomers can provide a basis for the synthesis of one single isomer. Negishi and Nozaki-Hiyama-Kishi reactions (Table 8) were developed where only the *E*-isomer reacted leaving the corresponding *Z*-isomer unreacted and facilitating the separation. This way, even the unreacted *Z*-isomer could be isolated with 89 and 62 % yield [20], [25].

Table 8: Negishi and Nozaki-Hiyama-Kishi reactions on the E-isomer of a 50:50 mixture [19], [20], [25].



Finally, other techniques that selectively react with either the *E*- or *Z*- form were developed like a selective reduction [26], [27] where mostly the *E*-isomer was reduced (Table 9). Repeated distillation could ultimately isolate the unreacted *Z*-form. Another methodology [20] was based on a selective dehydrobromination of the *Z*-isomer from *E*/*Z*-mixtures (Table 10). This way, the pure *E*-isomers could be created with good yield, based on the starting *E*-isomers.

Table 9: Selective reduction of the E-isomer [19], [26], [27].

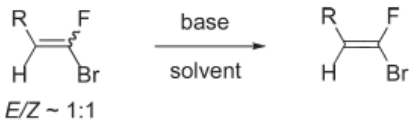


217 (*E*/*Z* - 1:1) (*Z*)-**217** (37-83%)[a] **252**

[a]Yield based on the amount of the (*Z*)-isomer in the starting *E*/*Z* mixture

R = Ph, 2-ClC$_6$H$_4$, 4-MeOC$_6$H$_4$, 1-naphthyl, Ph(Me)CH, *n*-C$_7$H$_{15}$

Table 10: Selective dehydrobromination of the Z-isomer [19], [20].



E/*Z* ~ 1:1

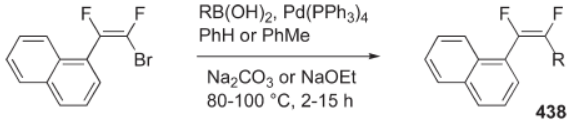
R[a]	base/solvent	yield (%)[b] (*E*)-isomer
$PhCH_2CH_2$	$LiN(SiMe_3)_2$/THF	88
$TBDPSOCH_2CH_2$	$LiN(SiMe_3)_2$/THF	98
4-$O_2NC_6H_4$	DBU/DMSO	55
4-$MeOC_6H_4$	DBU/DMSO	85
4-FC_6H_4	$LiN(SiMe_3)_2$/THF	67

[a]Only representative examples are reported.
[b]Based on starting (*E*)-isomer.

2.4.3 Cross-coupling reaction with organoboron partners

The current literature [7], [28]- [29] on cross-coupling reactions with boron reagents pays particular attention to the coupling of two aromatic systems. In Table 11 a Suzuki-coupling reaction was achieved with arylboronic and E-styrylboronic acid as coupling partners. Shimizu and co-workers [30] developed a completely stereoselective cross-coupling reaction. The same methodology was applied by McCarty and co-workers (Table 12) with various boronic acids resulting in high yields [31], [29].

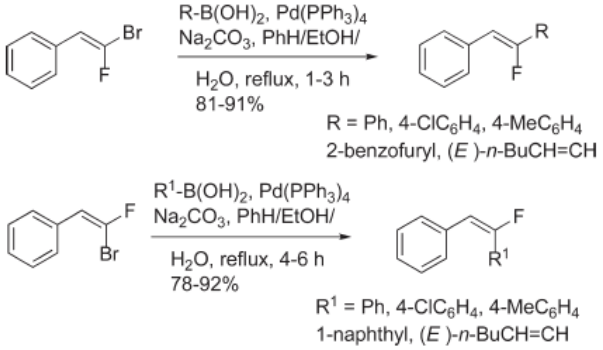
Table 11: Pd(PPh)$_3$-catalysed Suzuki coupling with boronic acids developed by Shimizu and co-workers [19], [30].



438

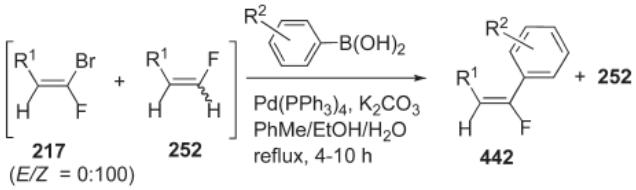
	R	**438** yield (%)
a	Ph	99
b	4-$MeOC_6H_4$	64
c	(*E*)-PhCH=CH	42

Table 12: Suzuki-coupling developed by McCarthy and co-workers [19], [31], [29].



By both varying the substituent of the starting material (R_1) and R_2 (substituent of the benzene ring on the boronic acid), a scope of the reaction was performed. The starting material of this reaction was obtained by a selective reduction and introduced in the Suzuki reaction (Table 13). This resulted in the desired product in a pure form, easily separated from the unreacted SM. Because the boronic acid could only react with a single isomer (**217**), the desired product (**442**) could easily be separated from the unreacted product (**252**) [7].

Table 13: Suzuki cross-coupling after a selective reduction was performed on the starting material [7], [19].



R^1	R^2	**442** yield (%)[a]
Ph	3-MeC(O)	83
2-ClC_6H_4	H	82
2-ClC_6H_4	3-NO_2	90
2-ClC_6H_4	3-Cl	90
1-naphthyl	H	85
PhCH(Me)	2-Cl	92
PhCH(Me)	3-MeC(O)	93

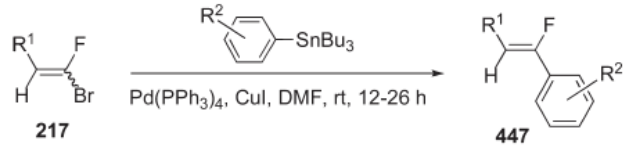
[a]Yield based on the amount of **442** in the starting mixture of **217** and **252**.

2.4.4 Coupling reactions with other reagents

Although all reactions in this research will be performed with boronic acids, the compounds could also be obtained with other coupling partners.

At first, organotin reagents can provide a new insight in the coupling reaction. These compounds react through a Stille reaction with high stereoselectivity, as shown in Table 14. A mixture with high *E*/*Z*-ratio could be coupled to obtain the desired product (**447**) with even higher *Z*/*E*-ratio [7], [27]. The coupling with an alkyltin coupling partner was also reported in the literature (Table 15) [22].

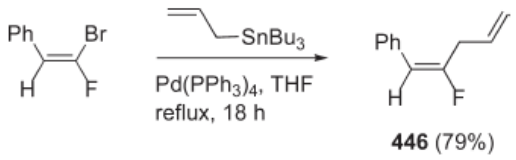
Table 14: Stille reaction on 1-bromo-1-fluoroalkene with high E/Z- rates [19], [7], [27].



217 *E/Z*	R^1	R^2	**447** yield (%)[a]	**447** *Z/E*
88:12	Ph	H	73	98:2
88:12	Ph	3-F	67	98:2
82:18	2-ClC_6H_4	H	71	94:6
82:18	2-ClC_6H_4	3-F	52	94:6
83:17	4-$MeOC_6H_4$	H	61	93:7
83:17	4-FC_6H_4	H	69	96:4
76:24	3-$O_2NC_6H_4$	H	53	87:13
88:12	3-ClC_6H_4	3-F	72	98:2
79:21	Ph(Me)CH	H	36	95:5

[a]Yield based on the amount of the (*Z*)-isomer in the starting *E/Z* mixture

Table 15: Stille reaction for the coupling of an aliphatic structure. [19], [22].



Organozinc reagents can be suitable coupling partners. An example (Figure 9) is a cross-coupling with a pure *E*- derivative of naphthalene as starting material. The reaction was performed with (4-methoxyphenyl)zinc(II) as catalyst, leading to the desired product with high yield [30]. Aliphatic zinc derivatives were also well tolerated. (Table 16). Literature [32] describes that catalysts $Pd_2(dba_3)$ and $PdCl_2(dppd)$ generated more yield, but the less-reactive $Pd(PPh_3)_4$ creates a better stereochemical outcome.

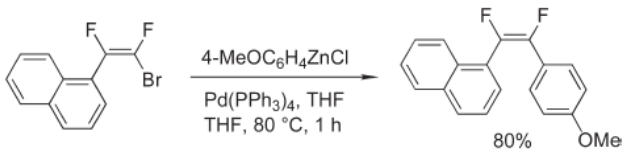
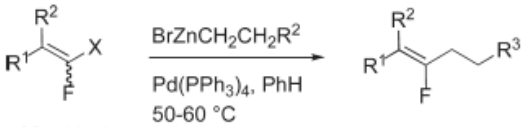


Figure 9: Negishi arylation with an organozinc reagent. [19], [30].

Table 16: Negishi cross-coupling on fluoro-alkenens [19], [32].



225: X = I
226: X = Br
227: X = Cl

458: $R^3 = CH_2CO_2Et$
459: $R^3 = CH_2CH{=}CH_2$
460: $R^3 = CH(OCH_2)_2$

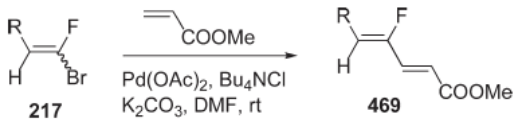
a: R^1 = Ph, R^2 = H; **b**: $R^1 = CH_2CH_2Ph$, R^2 = H
c: $R^1 = CH_2OCH_2Ph$, R^2 = H; **d**: R^1 = Ph, R^2 = Me

entry[a]	substrate(*E*/*Z*)	product (*Z*)	yield (%)
1	**225a** (95/5)	**458a**	70
2	**225a** (95/5)	**458a**[b]	93
3	**226a** (93/7)	**458a**	70
4	**227a** (93/7)	**458a**	80
5	**225a** (95/5)	**459a**	65
6	**225a** (95/5)	**460a**[b]	94
7	**225b** (84/16	**458b**[b]	82
8	**225b** (78/22)	**459b**	66
9	**225b** (15/85)	**460b**	14
10	**225c** (75/25)	**459c**[c]	56
11	**225c** (67/33)	**459c**[b]	86[d]
12	**225d** (49/51)	**458d**	45
13	**225d** (49/51)	**458d**[b]	60[e]
14	**225d** (49/51)	**459d**	45
15	**225d** (49/51)	**460d**	46

[a]Only representative results are reported.
[b]$PdCl_2(dppb)_2$ is used. [c]$Pd_2(dba)_2$ is used
[d]*E*/*Z* = 20/80. [e]*E*/*Z* =16/84.

Finally, alkenes can be coupled via a Heck reaction (Table 17). The reaction was performed with a starting material with high *E*/*Z*-ratio and the *E*/*Z*-ratio of the formed product could be further increased during the course of the reaction. The purification of the *Z*-isomer was more difficult due to their tendency to isomerize during the purification procedure [20].

Table 17: Heck reaction for the coupling of alkenes [19], [20].



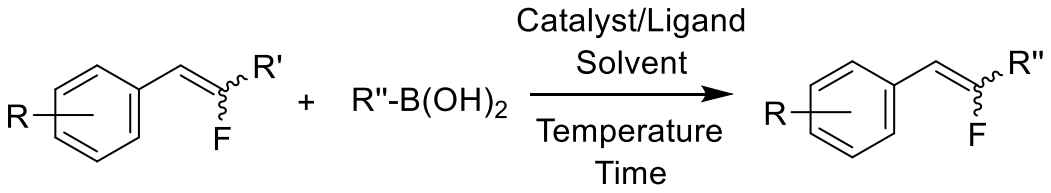
217 **469**

R	**217** *E/Z*	**469** yield (%)	(*E*,*Z*)/(*E*,*E*)[a]
Ph	85:15	70	95:5
2-ClC_6H_4	82:18	77	86:14
4-$MeOC_6H_4$	83:17	74	88:12
4-ClC_6H_4	88:12	82	96:4
4-FC_6H_4	87:13	78	91:9
3-$O_2NC_6H_4$	81:19	61	nd

[a]Ratio of the crude reaction mixture

3 RESEARCH QUESTION / PLAN OF ACTION

In order to develop an original methodology to obtain fluorinated compounds, this master's thesis will focus at first on the Suzuki-Miyaura reaction for the creation of alkylfluorostilbenes, as show in Reaction 5.

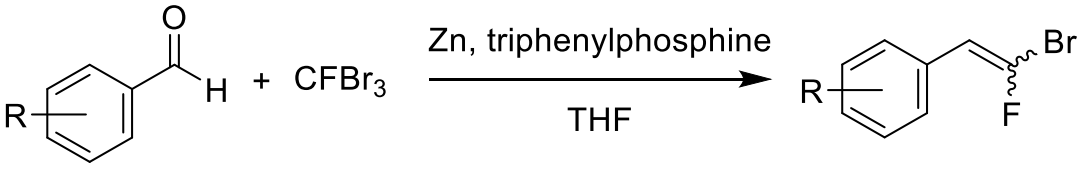


Reaction 5: General Suzuki-Miyaura reaction on alkylfluorostilbenes.

This research can be divided in three sections. At first, the synthesis of the starting material will be described. Next, the isomerization of (2-bromo-2-fluorovinyl)benzene will be studied. Finally, optimization of the Suzuki-Miyaura reaction will be presented as well as the scope of the Suzuki-Miyaura reaction.

3.1 Synthesis of the starting material

As previously mentioned, the substituents on the benzene ring have a huge impact on the outcome of the Suzuki-Miyaura cross-coupling reaction. In order to perform a study of the influence of these substituents, different starting materials were synthesized from the corresponding benzaldehydes through a Wittig reaction (Reaction 6) with triphenylphosphine and $CFBr_3$.



Reaction 6: General Wittig reaction to create each starting material of the Suzuki-Miyaura coupling.

3.2 Studies of the isomerism

Fluorostilbenes are usually formed as a mixture of *Z*- and *E*- isomers. It is crucial to know the forms and the ratio of the formed products. This can be determined by ^{1}H-NMR-spectroscopy of the synthesized product.

The problem however is the difficulty to synthesize only one isomer. This isomerization can possibly be achieved by a photo induced process with UV-light irradiation in combination with a photosensitizer. The effect of different photosensitizers (Figure 10) was investigated.

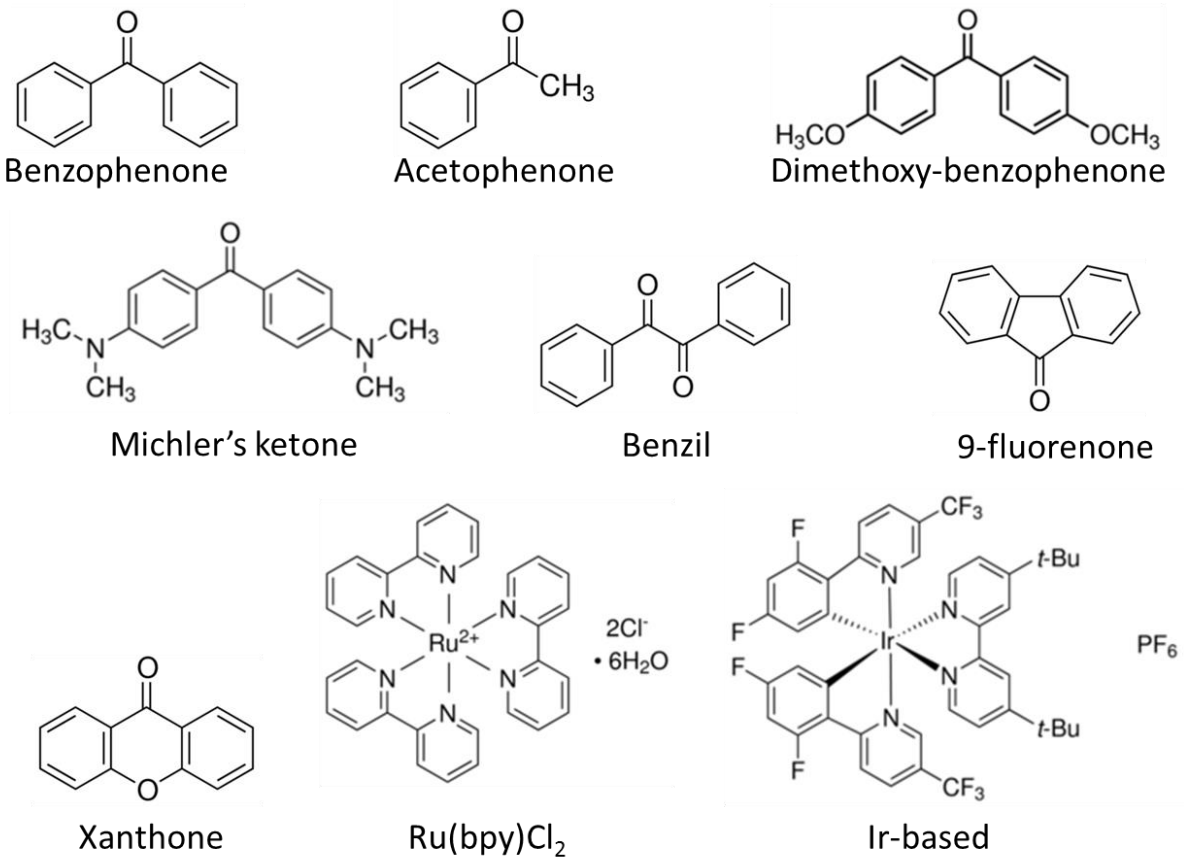


Figure 10: Nine different photosensitizers that could aid the isomerization with 365 nm UV-light.

Finally the possibility to perform the reaction in micro flow could be envisaged.

3.3 Optimization of the Suzuki-Miyaura cross-coupling

Based on previous studies (paragraph 2.3) the best solvent for the cross-coupling is a mixture of toluene and water. The base that gave the best results is Cs_2CO_3. Two catalytic systems show promising results. These are $PdCl_2$dppf (Figure 11) and $Pd_2(dba)_3$ in combination with Xantphos (Figure 12). This thesis performs practical experiments to finalize the optimum conditions in terms of yield and stereoselectivity.

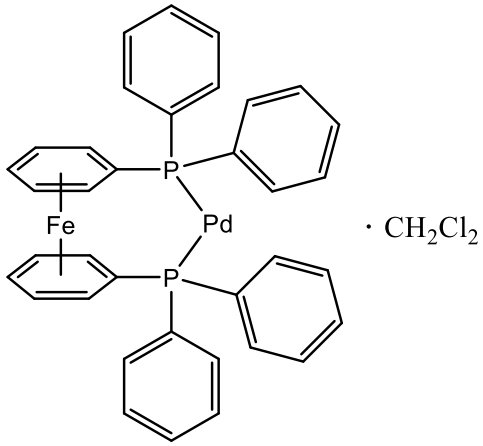


Figure 11: Chemical structure of $PdCl_2dppf.CH_2Cl_2$, the first catalytic system.

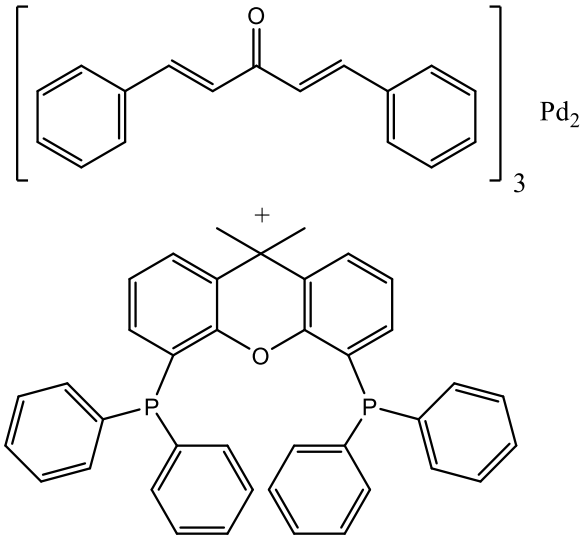


Figure 12: Chemical structure of $Pd_2(dba)_3$ and Xantphos, the second catalytic system.

The flexibility of the Suzuki-Miyaura reaction allows us to use a variety of boronic acids depending on the kind of aliphatic group we want to connect to the fluorostilbene. The general reaction on which all the variations are performed is with n-butane (Figure 13, left). However, changing the boronic acid could also have an effect on the yield and stereochemistry of the reaction and thus, could influence the choice in catalyst. For this reason, the Suzuki-Miyaura reaction is also performed with cyclopropane boronic acid (Figure 13, right).

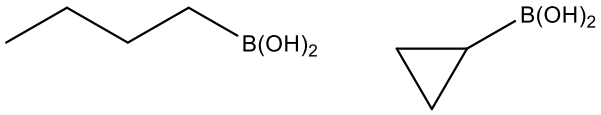


Figure 13: Examples of boronic acids that could be used in this study.

Furthermore, different substituents on the aromatic ring have impact on the outcome of the Suzuki-Miyaura reaction. These substituents are illustrated by "R" in the reaction and figures. Previous research at MSAP was performed on para-nitrofluorostilbenes. For the determination of the best catalyst, this -NO_2 substituent will be compared with an –OMe substituent and an unsubstituted alkylfluorostilbene. In this way, the effect of an electron donating and an electron withdrawing group can be compared with an unsubstituted form for both catalytic systems.

The effect of the temperature on the Suzuki-Miyaura reaction was also studied.

3.4 Scope of the Suzuki-Miyaura cross-coupling

The scope of the reaction will be done by varying the following substituents on the aromatic ring: -*p*-NO_2, -*p*-H, -*p*-OCH_3, -*p*-CF_3, -*p*-CO_2CH_3, -*p*-F, -*p*-Cl, -*p*-CH_3, -*o*-OCH_3 and -*m*-NO_2. Since -NO_2 and -OCH_3 are tested on two places, the effect of the position of the substituent can also be compared. For the effect of different substituents at different position on the aromatic ring determines the limitations of the reaction.

3.5 Objectives

To gain more insight into the Suzuki-Miyaura reaction on alkylfluorostilbenes, the above mentioned variations in boronic acid and aromatic substituents will be tested. A variation will have to fulfil the following criteria:

- A yield (after purification) of at least 80%, preferably 90%;
- The *Z*/*E* -ratio of the product must remain the same as the one of the starting material (*E*/*Z* -rate);
- No by-products formed (the fluorine-atom must remain on the product).

To finalize the optimization, the influence of the temperature and the catalytic system on the yield and the stereoselectivity will be investigated.

Considering the scope of the reaction, isolated yields (after column chromatography) of the products need to be obtained. A complete conversion is needed to obtain a yield as high as possible.

Isomerization of the generated products will be studied with the above mentioned photosensitizers. A successful isomerization has an *E*/*Z*-ratio of at least 95/5 or 5/95, so that the majority of the product consists of only one isomer.

4 MATERIAL AND METHOD

Organic reactions performed in this research are done under inert atmosphere, because the oxygen (in air) can disturb the reactions. To obtain this inert atmosphere, a Schlenk line is used (Figure 14). The Schlenk line allows switching the atmosphere between vacuum (Edwards RV3 pump) and inert Argon gas (Alphagar™ 1, Air Liquide®). The vacuum pump is protected by a trap cooled with liquid nitrogen.

Figure 14: Schlenk line equipment.

For liquid products, it's also necessary to create a bubble flow with a long needle to remove traces of air. For this reason, the solid products are always added first and the inert atmosphere is applied before liquid products are added to the mixture.

To evaporate the solvents used during the syntheses, two rotating evaporators are available in the laboratory (Figure 15). These are BUCHI Rotary Evaporators. The heating bath B-491 heats the round-bottom flasks to a temperatures around 35°C. The pressure is set by a Vacuum Controller V-850 and a Vacuum pump V-900. An internal cooling system (Isotemp®, Fisher Scientific) with isopropanol as cooling liquid is used to condensate the solvents after evaporation.

Chemical structures of the products can be analysed by Nuclear Magnetic Resonance spectroscopy (Bruker NMR AV300 – 300 MHz, Figure 16). NMR spectra give specific information about the nature of the compounds. In case of the ^{1}H-NMR spectra of alkylfluorostilbenes, two doublets around 6.5 ppm are present. These are the characteristic peaks of the *E*- and *Z*-isomer and are caused by coupling of the fluorine and hydrogen atom around the vinylic carbon-carbon bond. More information about these spectra and examples are given in paragraph 5 and in the Appendix.

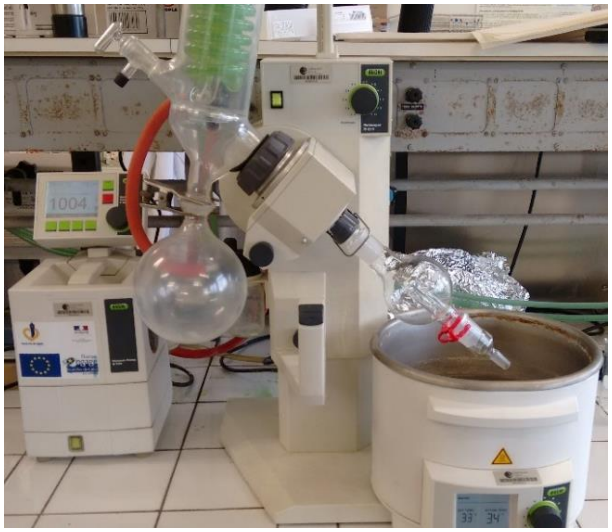


Figure 15: Rotary vacuum evaporator.

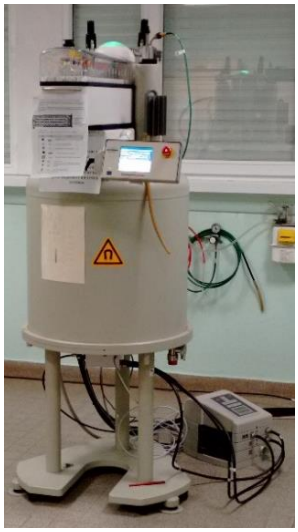


Figure 16: Bruker NMR AV300.

4.1 Synthesis of the starting material

The starting material can be synthesized via a Wittig reaction (Reaction 6). This reaction involves the use of an air-sensitive product, dibromoflouoromethane (CBr_3F). This means that the product will always be added lastly to the reaction mixture in inert atmosphere.

General procedure:

To a 100 ml round bottom-flask (with two or three necks) containing PPh_3 (1.2 equivalents, Alfa Aesar®) and Zn dust (1.2 equivalents, Janssen Chimica®), benzaldehyde ($1.00*10^{-2}$ mol) is added. One neck is then connected to a Liebig condenser and the other neck(s) are covered with rubber seal(s) (Figure 17, left). The Liebig condenser, at his turn is connected to a Schlenk line. The air is then sucked by the vacuum, before adding inert Ar. Next, THF (30 ml, Sigma-Aldrich®, pre-dried with activated molecular sieves 4 Å) and $CFBr_3$ (1.2 equivalents, Alfa Aestar®) are added with a syringe (thin needle can penetrate the rubber seals). The reaction vessel is heated (80°C) in an oil bath and stirred magnetically (300 rpm) by an IKA® C-MAG HS 7 or an IKA® RET basic steering and heating plate. The heating liquid is Thermal HL45- oil which had a temperature range between -45 °C and +250 °C. The reaction time is always 15 hours.

Figure 17: Setup of the Wittig reaction (left) and purification steps (vacuum filtration in the middle and column chromatography at the right).

After the reaction, the flask is cooled to room temperature. The purification involves first a vacuum filtration with Celite© 545 (SiO_2, Acros Organics) and ethyl acetate as solvent (Figure 17, middle). Next the solvent is evaporated and the product is dissolved in small quantities of DCM. This product can then be purified by Silica gel 60 column chromatography (0.063-0.2 mm, Macherey-Nagel) with petroleum ether as eluent. The separation principle is based on the polarity of the products. The experiment starts with an eluent of 100% petroleum ether (220 ml), after which the polarity is

gradually increased by adding more ethyl acetate. One ml of EtAc is additionally added per 44 ml solvent, until the petroleum ether/EtAc volume ratio is 61/39. The collected fractions are tested with Merck TLC Silica gel 60 F_{254} to confirm the elution of the product. A new NMR experiment (in $CDCl_3$) will then confirm the chemical structure. The yield is calculated gravimetrically (by weighing the mass of a round-bottom flask, with and without the purified product).

4.2 Isomerization

The isomerization (Reaction 2) will be performed with the aid of a photosensitizer and UV-light irradiation. The nine different photosensitizers are described in paragraph 3.2. UV-light of 365 nm is realized by an OmniCure® AV7300 UV LEDs at 100% intensity (250 $mW.cm^{-2}$). Samples are always placed at a distance of 10 cm from the lamp.

As the isomerization will be performed in batch, as well as in flow, both procedures are described.

General procedure of isomerization in batch for 40.0 g product:

To a test tube, 40 mg of a (2-Bromo-2-fluorovinyl)benzene derivative, a photosensitizer (0.1 equivalents) and a solvent (2 ml, toluene at first) is added. After adding a magnetic stirring bar, the test tube is firmly tightened by a rubber seal. The solution is then degassed by purging Ar through the solution and afterwards above the liquid.

Next the tube is placed in the isomerization setup (Figure 18) at a distance of 10 cm from the lamp. The solution is stirred with a magnetic stirring bar at 300 rpm with the IKA® RET basic 2 steering plate (no heating enabled). Up to five tubes can be placed in this setup to remain good radiation and stirring properties. The tests in batch are all performed without temperature control, because a heating or cooling bath could interfere with the radiation of the UV light.

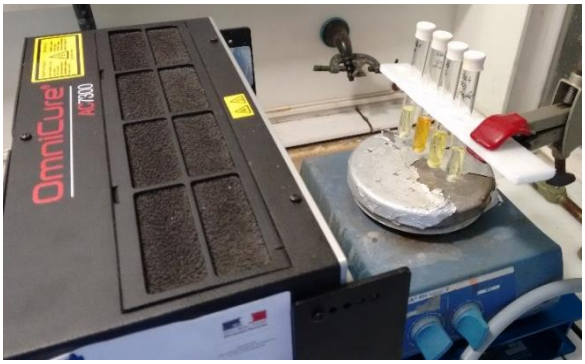


Figure 18: Setup of isomerization in batch.

If sampling is required, a sample of 0.25 ml can be taken with a long syringe. Before the UV-radiation is switched on for further testing of the remaining solution, the solution will be degassed with Ar as described above. The 0.25 ml sample is put in a 50 ml round-bottom flask for evaporating the solvent with the rotary vacuum evaporator. Next, the sample is transferred to an NMR tube with the aid of 0.8 ml $CDCl_3$ and will be analysed by ^{1}H-NMR spectroscopy.

If a single-run test is performed (no sampling), the entire solution will be transferred to a 50 ml round-bottom flask with the aid of DCM. 1,3,5-triethoxybenzene (1 equivalent) will be added as internal standard and the solution is evaporated under vacuum. A ^{1}H-NMR spectroscopy experiment in 0.8 ml $CDCl_3$ is performed to determine the *E*/*Z*-ratio.

General procedure of isomerization in flow for 40.0 g product:

To a 100 ml double neck round bottom flask, 40 mg of a (2-Bromo-2-fluorovinyl)benzene derivative, a photosensitizer (0.1 equivalents) and a solvent (2 ml, toluene at first) is added.

For the removal of oxygen, the small neck is connected to a Schlenk line while the larger neck is covered with a rubber seal (Figure 19). The solution is then frozen with liquid nitrogen. Next, the Schlenk line is switched to the vacuum pump to suck the gas above the solid. Then, when the solid is melted, an inert atmosphere is created. This procedure is repeated two more time to make sure that every trace of oxygen is removed.

In the next step, the solution is sucked into an 8 ml stainless steel syringe with a SWAGELLOCK® connector. The syringe is covered by a seal and this replaced the seal of the flask. During the replacement of the seals, a large flow of Ar gas is enabled to make sure that oxygen doesn't contaminate the solution.

The syringe is then placed on a Harvard Apparatus Standard Infuse/Withdraw PHD^{TM} ULTRA syringe pump in the flow setup (Figure 20) and connected to the photo-microreactor. This reactor is a dwell-reactor manufactured by Microglass Chemtech Mainz (Germany) with rectangular shape of dimensions 115 mm x 2 mm x 0.5 mm. The exit of the microreactor is connected to a 50 ml round bottom flask, covered by aluminium foil to prevent isomerization of the product after it left the reactor. A constant temperature of 20 °C is maintained by the flow of water through separate channels in the reactor that are connected to a heating/cooling device (Amersham Biosciences MultiTemp III). The residence time can be controlled by adjusting the flow rate of the pump (irradiation time = residence time), as explained in paragraph 1.6. The 365 nm UV-lamp is placed at a distance of 10 cm from the microreactor.

Figure 19: Degassing of the solution for flow trials.

Figure 20: Setup of isomerization in flow.

The light source and the pump are turned on at the same time. When the residence time (irradiation time) is finished, the syringe is switched with a syringe that only contains the solvent. The solvent is then pumped in the reactor to wash out the product at the same flow rate as before. The lamp is switched back simultaneously with the pump.

Finally, 1,3,5-triethoxybenzene (1 equivalent) will be added as internal standard and the solution is evaporated under vacuum. A ^{1}H-NMR spectroscopy experiment in 0.8 ml $CDCl_3$ is performed to determine the *E*/*Z*-ratio.

4.3 Suzuki-Miyaura cross-coupling: optimization and scope

The Suzuki-Miyaura reaction is presented in Reaction 5 at paragraph 3.

General procedure for the reaction of 60.0 mg starting material:

A 100 ml round bottom-flask (with two or three necks and stopcock) or a Schlenk flask (50 – 100 ml) with side stopcock (Figure 21) is used for the reaction. First, the solids are added: Cs_2CO_3 (3 equivalents, Aldrich), $BuB(OH)_2$ (1.2 equivalents, Aldrich) or isopropyl boronic acid (1.2 equivalents, Fluorchem) and the catalytic system. The first catalytic system is $PdCl_2$dppf (2 mol %, Fluorochem Ltd) and the second consists of $Pd_2(dba)_3$ (2 mol %, Fluorochem Ltd) in combination with Xantphos (2 mol %, Aldrich). If the SM is a solid, it is also added. The stopcock is than connected to a Schlenk line, while the neck(s) are covered with rubber seal(s). The air is then removed by vacuum, before adding inert Ar-gas. Next the liquids are added (thin needle can penetrate the rubber seals): SM (60.0 mg, 1 equivalent), toluene (2.2 ml) and MilliQ water (0.25 ml). The heating and stirring system is the same as described in paragraph 4.1. The reaction time varies between 1, 3 and 6 hours.

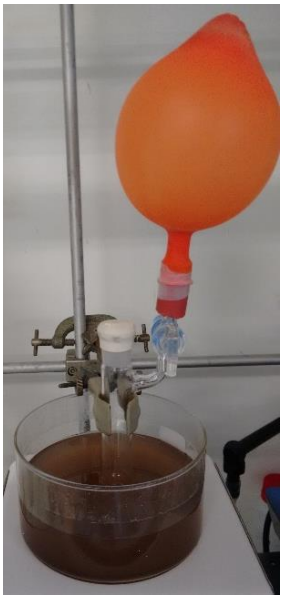


Figure 21: Setup for cross-coupling reaction

When the reaction is completed, an extraction with dichloromethane is performed (three times) and the organic phase is washed with MiliQ water, dried by adding $MgSO_4$ (Acros Organics) and filtered on hydrophilic cotton (100%). The solvents are removed under vacuum. Next, a small part of the product (5-10 mg) is dissolved in $CDCl_3$ for NMR experiments to monitor the reaction. To avoid losing product, the NMR sample is recovered.

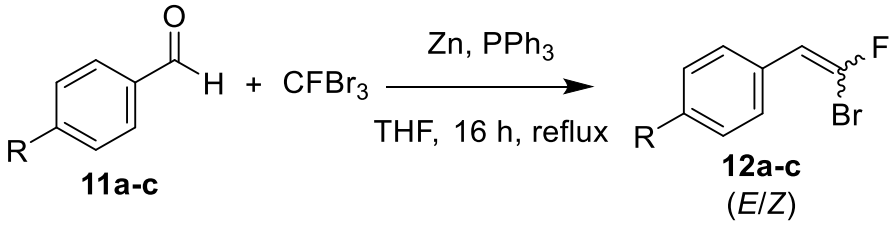
After the previous step, a relatively clean product is obtained. However, it still contains traces of both aromatic (starting product, degraded products or catalysts) and aliphatic impurities (solvents, grease or degraded products) that are visible by NMR spectroscopy. An automatic silica column chromatography at the Interchim PuriFlash© 215 is performed to remove these impurities. The column consists of 4 gram Normal Phase High Performance Silica (Interchem, 30 µm). The eluent starts with 100 % petroleum ether (for 5 minutes) and ethyl acetate is gradually added for 8 minutes until a mixture of 95 % petroleum ether and 5 % EtAc is reached. Detection with a 254 nm LdO-UV confirms the elution of the product. A new NMR test in $CDCl_3$ will then confirm the purity of the product. The yield is calculated gravimetrically.

Figure 22: automatic chromatography equipment.

5 RESULT AND DISCUSSIONS

5.1 Starting material

The starting material for the Suzuki-Miyaura reaction can be synthesized though a Wittig reaction with $CFBr_3$, Zinc and triphenylphosphine (Reaction 7). The procedure is described in paragraph 4.3.



Reaction 7: Wittig reaction on aldehydes to synthesize dihalogenated stilbenes.

The results of these reactions are given in Table 18. Yields of 24-42 % were achieved after purification by column chromatography.

Table 18: Results of the Wittig reactions after purification.

Entry	-R	*E/Z*	Yield (%)
a	p-NO_2	58/42	39
b	p-CF_3	50/50	24
c	p-$COOCH_3$	45/55	42

During a second synthesis, starting material **12a** (*p*-NO_2) was washed with a small amount of petroleum ether (bp: 40-65°C), just enough to partly dissolve the solid. The solid residue contained the product with an *E*/*Z*-ratio of 87/13. On the other hand, the dissolved solid in the filtrate contained **12a** with an *E*/*Z*-ratio of 21/79 and some impurities. Thus, this method allowed us to obtain a product enriched by the *E*-isomer, that could be interesting to use in the Suzuki-Miyaura cross-coupling.

Other starting material available in the laboratory are listed in Table 19.

Table 19: Starting material for the Suzuki-Miyaura reaction synthesized by Laetitia Chausset-Boissarie.

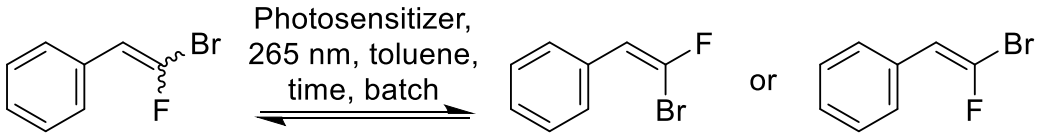
Substituent	*E/Z*
-*p*-H	47/53
-*p*-OCH_3	48/52
-*p*-F	48/52
-*p*-Cl	47/53
-*p*-CH_3	49/51
-*o*-OCH_3	41/59
-*m*-NO_2	53/48

5.2 Isomerization

5.2.1 9 photosensitizers at long term.

During the first set of experiments, 9 different photosensitizers were used under 365 nm UV-light irradiation (Reaction 8). (2-bromo-2-fluorovinyl)benzene with an *E*/*Z*-ratio of 47/53 was used as starting material.

Because oxygen could have an impact on the isomerization, all reactions were performed under inert atmosphere and all liquids were degassed by purging the reaction mixture with Ar-gas.



Reaction 8: First isomerization trials of (2-bromo-2-fluorovinyl)benzene.

Figure 23 shows the percentage of the *E*-isomer of the *E*/*Z*-ratio as function of the reaction time. The test was stopped at 20 min, 40 min, 1 hour, 2 hours and 12 hours. However, only results until 2 hours are shown for comparability purposes. This means that the top of the curve shows results of an almost pure *E*-isomer and at the bottom of the curve almost pure *Z*-isomer.

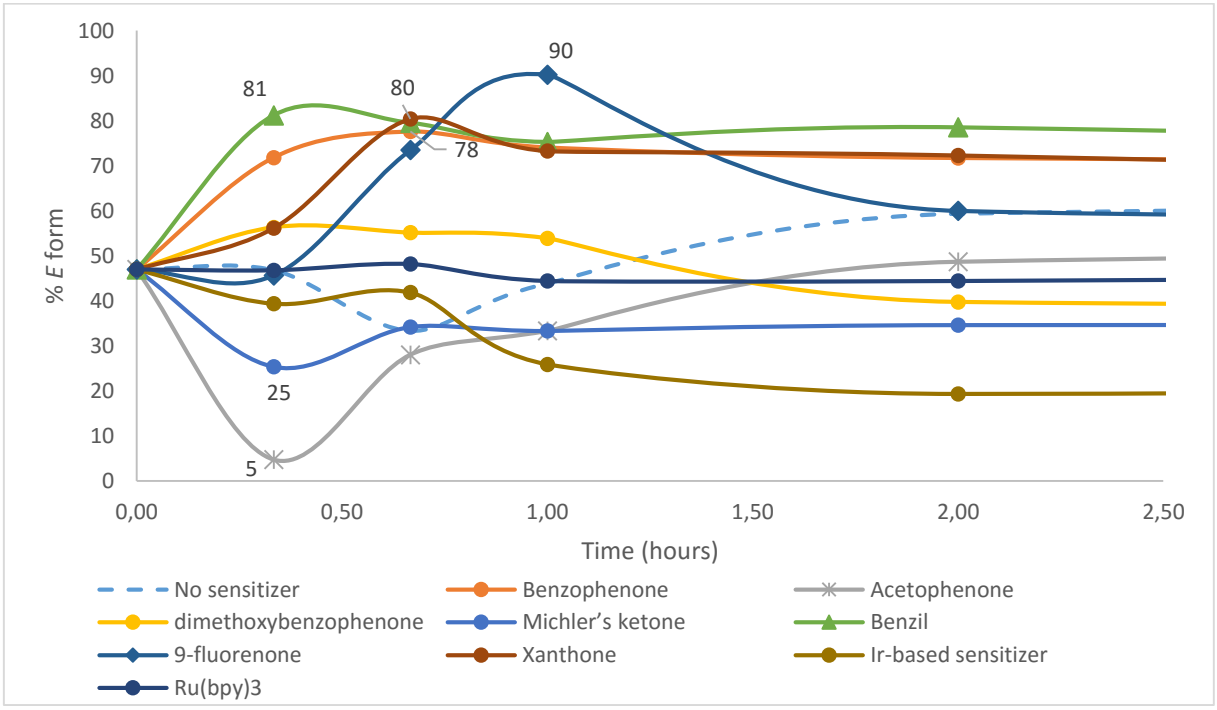


Figure 23: Percentage of the E*-isomer as function of the reaction time for the first isomerization reaction on 2-bromo-2-fluorovinyl)benzene in toluene with 9 different photosensitizers under 365 nm UV light irradiation.*

The best results towards an *E*-isomer were obtained with Benzil (81/21 at 20 min), Xanthone (80/20 at 40 min), Benzophenone (78/22 at 20 min) and 9-fluorenone (90/10 at 1 hour). 9-fluorenone has an *E*/*Z*-ratio that is close to the desired ratio of 95/5. The best results towards the *Z*-isomer are obtained with Acetophenone (5/95 at 20min). It seems that there is an optimal reaction time for each sensitizer.

5.2.2 *Influence of oxygen*

To test the influence of oxygen, an isomerization (Reaction 8) with Benzil as photosensitizer under inert atmosphere was compared with an experiment with Benzil as photosensitizer in an open test tube (exposed to air). The test without the use of a sensitizer is also presented in the dotted line (Figure 24).

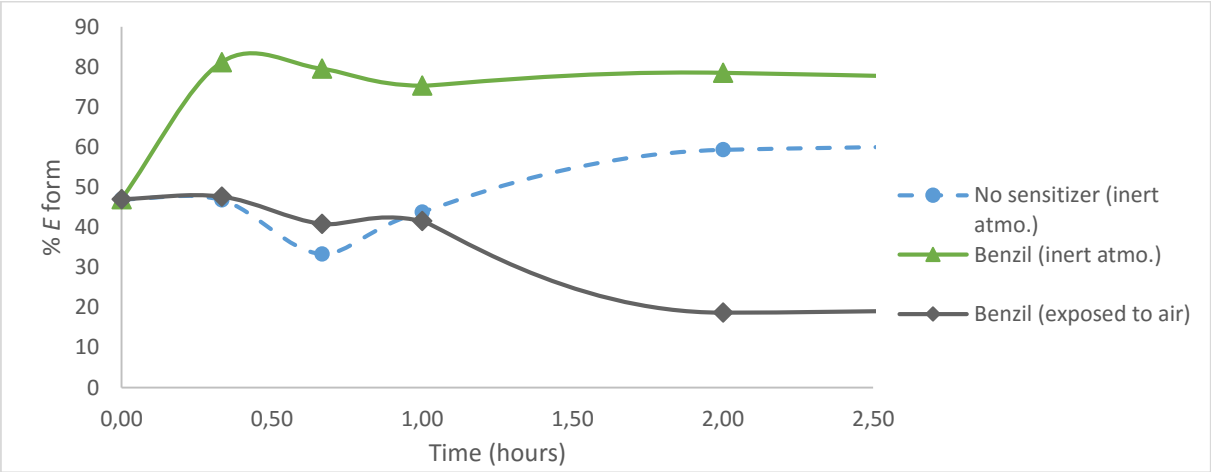


Figure 24: Percentage of the E-isomer as function of the reaction time for the isomerization of 2-bromo-2-fluorovinyl)benzene in toluene with benzil-photosensitizer and 365nm UV-light under inert atmosphere and exposed to air.

At first, when the product exposed to air (dark line, Figure 24)is irradiated, only few isomerization occurs. After one hour the isomerization seem to shifts towards the *Z*-isomer. This result is only obtained because of degradation of the product. The degradation of the *E*-isomer seems to be favoured over the *Z*-isomer, resulting in a shift in the *E*/*Z*-percentage. Figure 25 shows a variety of peaks that will appear in the NMR-spectra (circled blue) as degradation occurs. These peaks can become bigger than the peaks of the desired product (5.7 – 6.4 ppm).

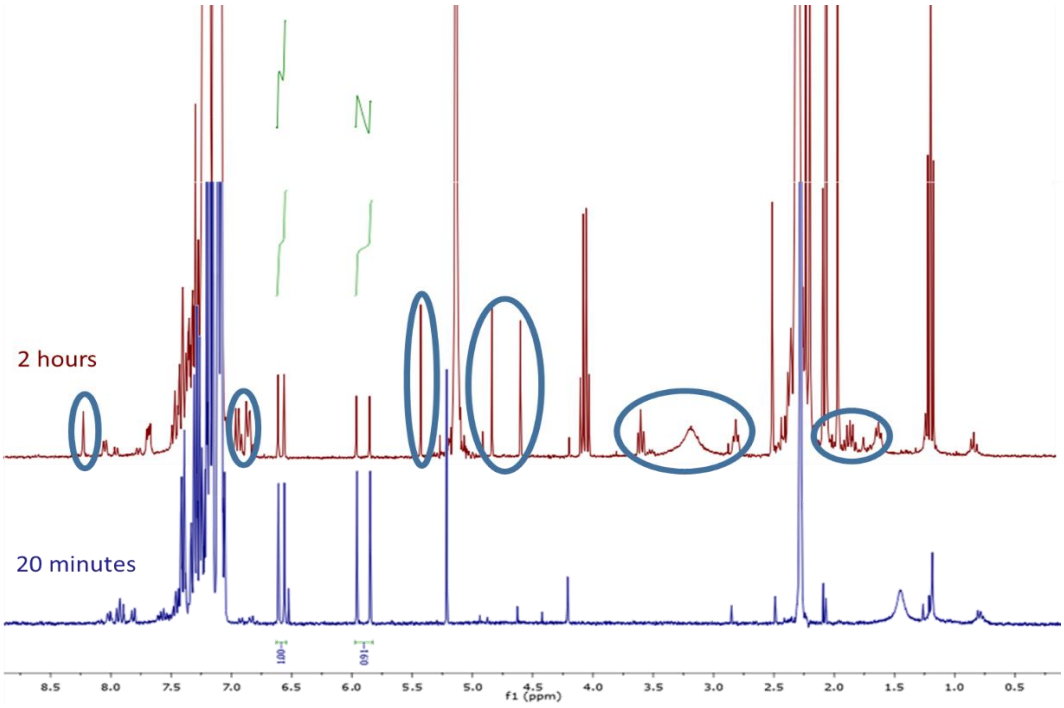


Figure 25: Comparison of ^{1}H-NMR spectra for the isomerization of 2-bromo-2-fluorovinyl)benzene with benzil under 365 nm UV-light at 20 min and 2 hours.

5.2.3 Short-term isomerization

After the promising results of photosensitizers acetophenone (for the *Z*-isomer) and benzil (for the *E*-isomer) at 20 minutes irradiation time, a reduction in reaction time was researched. Thus, the same isomerization (Reaction 8) was monitored at 2, 4, 8, 15 and 20 minutes.

The results (Figure 26) show almost no change in the *E*/*Z*-ratio when acetophenone is used with a short reaction time. The best result is an *E*-percentage of 44 %. As the starting material has 47 % of the *E*-isomer, there is only a small improvement of 3 % towards the *Z*-isomer. This is a completely different result compared with the first set of experiments with acetophenone (Figure 23), which questions the reproducibility of the reaction. Further trials need to be performed to rationalize this experiment.

The results (Figure 26) with Benzil were a little bit more promising. The best result was an *E*-percentage of 71%. There is still much improvement necessary to obtain the desired 95%. As with acetophenone, we found some reproducibility issues and more research needs to be performed to achieve a reproducible result.

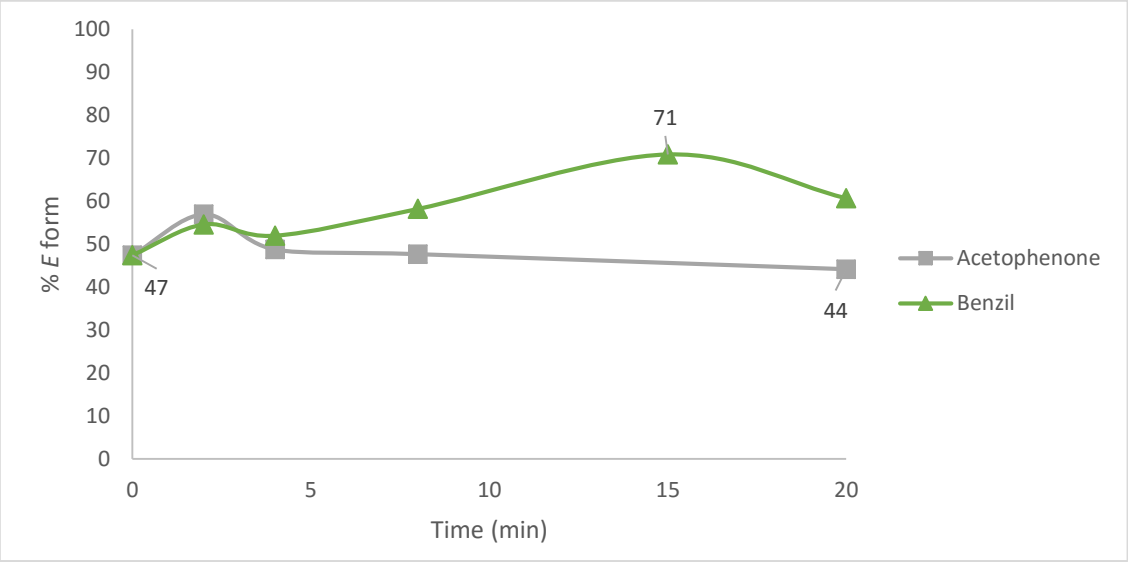


Figure 26: Percentage of the E*-isomer as function of the reaction time for the isomerization of 2-bromo-2-fluorovinyl)benzene in toluene with benzyl and acetophenone as-photosensitizer and 365nm UV-light under inert atmosphere.*

A possible explanation might be a contamination with oxygen (paragraph 5.2.2) during the sampling. Although after each sampling an Ar-flow was used to remove the possible contamination of oxygen, traces might still be present. To remove the influence of sampling, a new trial will be performed (Single run tests, paragraph 5.2.4).

Another possible explanation might be the influence of temperature. The previous trails (in batch) are performed at room temperature. Since the irradiation is performed with HP UV LEDs which heat up the test tubes during the course of the reaction, it's difficult to control the temperature. The correct temperature can't be measured and varies throughout the experiment. In batch, the temperature can't be controlled by a heating/cooling bath, because this would interfere with the radiation. However, new trials will be performed in a flow system where the temperature can be controlled (paragraph 5.2.7).

5.2.4 Single run tests

The varying results observed in the previous experiments might suggest that sampling could have a negative effect on the isomerization (paragraph 5.2.1 & 5.2.3). Performing tests without sampling (single run) take more time, because the whole procedure needs to be performed for each result.

On the other hand, an advantage of a single run-test is the possibility to calculate the yield by adding an internal standard. 1-bromo-4-methoxybenzene was used as the internal standard and was added after the reaction because it can possibly interact with the isomerization reaction.

Table 20 shows the results of the single run for the isomerization with acetophenone. For the second time a low effect on the isomerization towards the *Z*-isomer was obtained. This photosensitizer will be excluded from further trials. As for Benzil and 9-fluorenone, both show isomerization towards the *E*-isomer. However, the percentage of the *E*-isomer from the test with 9-fluorenone is 8 % lower than the first time (82 instead of 90 %). Further trails needs to be performed to confirm the reproducibility of 9-fluorenone. The NMR-yield of the samples are approximately the same.

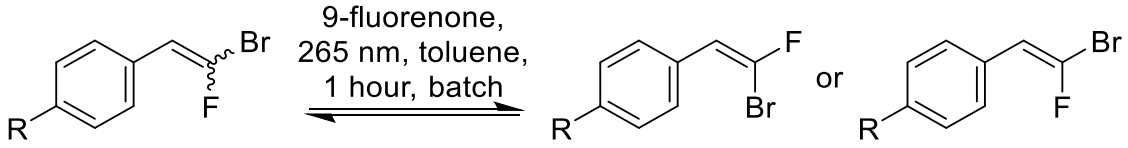
Table 20: Single run tests on the three most promising photosensitizers (365 nm UV light, toluene).

Sensitizer	Percentage of the *E*-isomer			NMR Yield
	0 min	20 min	1 hour	%
Acetophenone	47	43	-	78
Benzil		81	-	74
9-fluorenone		-	82	73

A complete overview of all the trials with acetophenone at 20 min, benzil at 20 min and 9-fluorenone at 1 hour is given in Table 24.

5.2.5 Influence of the substituents

To gain more knowledge about the reaction, the influence of the electronic effect of different substituents on the aromatic ring will be studied. Results of Reaction 9 are presented in Table 21.



Reaction 9: Isomerization reaction to determine the influence of the substituents on the benzene ring.

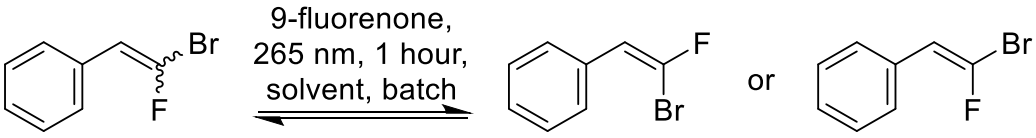
Through a reaction with the unsubstituted starting material, 60 % of the *E*-isomer was obtained. No real trend was noticed between the *E*/*Z*-ratio and the electronic properties of the substituents. This demonstrates that we did not find a general photosensitizer and more investigation needs to be done.

Table 21: Isomerization trials to determine the influence of the substituents on the benzene ring.

Substituent (-R)	Electronic effect	SM *E/Z*	Prod. *E/Z*	NMR-Yield %
-H	None	47/53	60/40	78
-NO_2	Deactivating	50/50	34/66	97
-OMe	Activating	48/52	53/47	86
-NO_2	Deactivating	87/13	32/68	96

5.2.6 Influence of the solvent

Finally, the influence of the solvents on the isomerization is studied. Previous isomerization reactions were performed in toluene because this solvent is also used in the Suzuki-Miyaura cross-coupling reaction. The isomerization Reaction 10 was performed, which uses 9-fluorenone as photosensitizer.



Reaction 10: Isomerization reaction to determine the influence of the solvent.

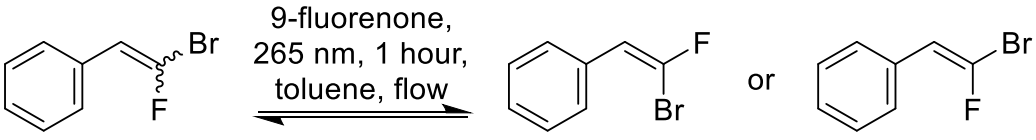
The results (Table 22) show low isomerization in methanol. Acetonitrile or dichloromethane give slightly better isomerization than toluene. Reactions with toluene resulted in *E*/*Z*-ratios of 90:10, 82:18 and 60:40. Considering that toluene is used in the Suzuki-Miyaura reactions, it would be better to stay in the same solvent to perform the isomerization.

Table 22: Isomerization (Reaction 10) trials to determine the influence of the solvent.

Solvent (E/Z SM = 47/53)	Prod. *E/Z*	Yield %
Methanol	46:54	74
Acetonitrile	82:18	77
DCM	83:17	84
THF	77:33	74

5.2.7 Flow setup

The object of the isomerization is to obtain only one isomer or at least 95% of one isomer. The photosensitizer which has the best results so far is 9-fluorenone. That's why the next trials will be performed with 9-fluorenone.



Reaction 11: Isomerization reaction in flow setup.

Flow configurations have the advantage to maintain a constant temperature thanks to the cooling/heating channels of the flow reactor. The temperature was set at 20°C. Thus, the heating effect of the UV-light could be eliminated.

Results of the trials with flow condition are shown in Table 23. The percentage of the *E*-isomer changes only from 47% towards 53%.

Table 23: Results of the isomerization reaction in flow with the aid of 9-fluorenone, 365 nm UV light (in toluene at 20°C).

	9-fluorenone in flow					
time (min)	**0**	**2**	**4**	**6**	**10**	**20**
% *E*-from	47	52	47	50	53	45
Yield (%)	-	31	8	12	8	9

The yields are also very low for these trials due to degradation of the starting material or loss of product. The low isomerization could be explained by the absence of temperature rise. Maybe the isomerization actually needs a higher temperature to take place.

Future prospects for the isomerization are to perform the reaction at a constant higher temperature (40 °C or 60 °C) to see the impact on the isomerization rate. Unfortunately, this could not be performed in practice due to a limited time range of the internship and the higher priority of the Suzuki-Miyaura coupling reactions.

5.2.8 Conclusion isomerization

Table 24 gives a summary of all the trials that have been performed with acetophenone, benzil and 9-fluorenone at the most promising reaction times (20 minutes or 1 hour) in batch.

Table 24: Summery of all the trails on (2-bromo-2-fluorovinyl)benzene in batch (solvent = toluene, UV-light = 365 nm, inert atmosphere).

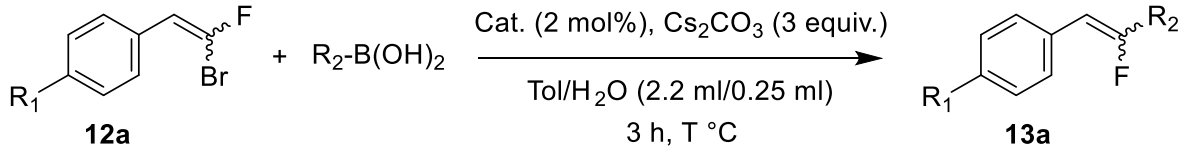
Trial	**Paragraph**	**Percentage of the *E*-isomer**		
		Acetophenone 20 min	**Benzil 20 min**	**9-fluorenone 1 hour**
Long term	5.2.1	5	81	90
Short term	5.2.3	44	61	-
Single run tests	5.2.4	43	81	82
Substituent	5.2.5	-	-	60

Although the first test with acetophenone resulted in a good isomerization towards the *Z*-isomer. This result was unfortunately not reproducible as for the use of 9-fluorenone. At this point, benzil seem to give the most reproducible results of the three photosensitizers.

In conclusion, none of the above trials could meet the criteria of an *E*/*Z*-ratio of 95/5 or 5/95. However, promising results were obtained with benzil and 9-fluorenone, since an isomerization towards the *E*-form could be obtained in combination with 365 nm UV-light irradiation. Each photosensitizer has an optimal reaction time. Further experiments are necessary to solve the reproducibility issues and improve the E/Z ratio.

5.3 Optimization of the Suzuki-Miyaura

As mentioned in the literature review (paragraph 2.3), the best solvent to perform the Suzuki-Miyaura for alkyfluorostilbenes is toluene/H_2O in a ratio of 10/1 and the best base is Cs_2CO_3. These two parameters will be used for the Suzuki-Miyaura cross-coupling (Reaction 12). Notice that *E*/*Z*-1 of product **2a** will turn in *Z*/*E*-2 of product **3a** after the reaction.



Reaction 12: Optimization of the Suzuki-Miyaura cross-coupling.

To determine the best temperature and catalytic system for the Suzuki-Miyaura cross-coupling, parameters are varied. All the results with variations are summarized in one table (Table 25). In the next paragraphs, the parameters will be explained separately.

Table 25: Results of the optimization of the Suzuki-Miyaura cross-coupling after a reaction time of 3 h.

Entry[a]	-R_1	Pd catalyst	*E*/*Z*-12[b]	R_2	Temp.	*Z*/*E*-13[b]	Conv. (%)	Yield (%)
1	-NO_2	$PdCl_2dppf$	50/50	Butyl	RT	-	0	-
		Pd_2dba_3/Xantphos				-	0	-
2	-NO_2	$PdCl_2dppf$	50/50	Butyl	60°C	45/55	>50	51[d]
		Pd_2dba_3/Xantphos				48/52	>50	29[d]
3	-NO_2	$PdCl_2dppf$	55/45	Butyl	80°C	45/55	100	97[c,e]
		Pd_2dba_3/Xantphos	46/54			51/49	100	86[c,e]
4	-NO_2	$PdCl_2dppf$	50/50	cyclo-propyl	80°C	65/35	100	82[e]
		Pd_2dba_3/Xantphos				43/57	100	>35[e]
5	-H	$PdCl_2dppf$	47/53	Butyl	80°C	50/49	100	38[e]
		Pd_2dba_3/Xantphos				47/53	95	44[e]
6	-OCH_3	$PdCl_2dppf$	48/52	Butyl	80°C	49/51	100	70[e]
		Pd_2dba_3/Xantphos				40/60	100	68[e]
7	-NO_2	$PdCl_2dppf$	87/13	Butyl	80°C	83/17	100	93[e]

a) All the reactions were performed under inert atmosphere. b) The *E*/*Z*-ratio was determined from ^{1}H-NMR spectroscopy, thanks to characteristic doublets of the vinylic proton around 6 ppm. c) Results obtained through previous research [17]. d) An internal standard was added to calculate NMR yields. e) Isolated yields were obtained after purification of the product by column chromatography on silica gel.

When comparing the *E*/*Z*-ratios of the starting material, one should keep in mind that the *E*/*Z*-ratio changes throughout the reaction because of the loss of bromine. For example, the *E*-isomer will change into the *Z*-isomer (paragraph 1.5). For this reasons, the isomerism of the product is illustrated as *Z*/*E* instead of *E*/*Z*, which allows better comparing the results.

5.3.1 Temperature

The first entry of Table 25 shows that the reaction does not take place at room temperature (RT). This means that a temperature of about 25°C cannot deliver the required energy to pass the energy barrier of the reaction.

At 60°C (entry 2 of Table 25) the reaction takes place very slowly. Low conversion is observed, leading to low NMR-yields (29-51%). Because of the low NMR-yields at 60°C, the temperature will be maintained at 80°C in further tests.

5.3.2 Catalysts

For the determination of the best catalyst for the cross-coupling reaction, experiments were performed with slight variations of boronic acid (entry 4 of Table 25) and para-substituents on the aromatic ring (entry 5 and 6 of Table 25) as coupling partners.

Experiments performed with $PdCl_2$dppf as catalyst gave generally better yields than the Pd_2dba_3/Xantphos catalytic system. An exception is the synthesis of (2-butane-2-fluorovinyl)benzene (substituent = -H, entry 4 of Table 25). Pd_2dba_3/Xantphos led to 6% more yield than the synthesis with $PdCl_2$dppf.

Depending on the substituent on the aromatic ring, the reaction is not always complete after three hours. The rate of the reaction with $PdCl_2$dppf seems higher compared to Pd_2dba_3/Xantphos.

The stereoselectivity is also an important factor in the choice of the best catalytic system. For this the *E*/*Z*-ratio of the starting materials is compared with the *Z*/*E*-ratio of the products. A retention of stereochemistry is best achieved with the Pd_2dba_3/Xantphos catalytic system. The only exception is entry 6 of Table 25.

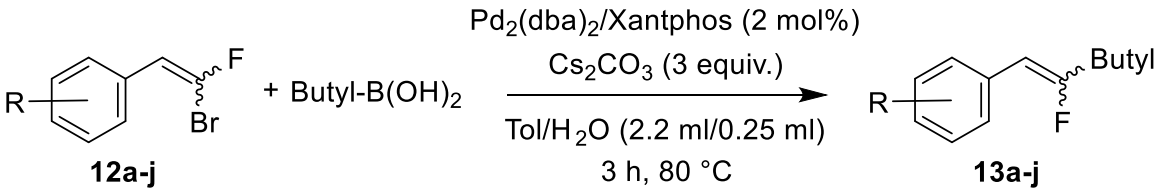
In conclusion, the rate is the reaction is higher with $PdCl_2$dppf, but the reaction is more selective with Pd_2dba_3/Xantphos. Since this parameter is more crucial, Pd_2dba_3/Xantphos will be the catalyst of choice for further studies.

5.3.3 Starting material enriched with the E-isomer

As an extra experiment a cross-coupling reaction was performed with a starting material with higher *E*/*Z*-ratio. Paragraph 5.1 explains the synthesis of this -*p*-NO_2 substituted starting material with an *E*/*Z*-ratio of 87/13. The reaction performed with $PdCl_2$dppf as catalyst, generated a product with 4 % less *Z*-isomer (entry 7 of Table 25).

5.4 Scope of the Suzuki-Miyaura

To determine the limitations of the reaction a scope of the reaction was performed (Reaction 13). The scope included functional groups in para, meta and ortho position with both mesomeric electron withdrawing and donating groups (-NO_2, -CO_2Me, -OMe), inductively donating groups (-Me) together with both mesomeric donating and inductively withdrawing halogens (-F, -Br). The experiments are sorted by increasing reaction time in the next paragraphs.



Reaction 13: Scope of the Suzuki-Miyaura cross-coupling.

5.4.1 One hour reaction time

The Suzuki-Miyaura was performed for 1 hour to see if the reaction time could be reduced (Table 26). The reaction was not completed at this reaction time. At this stage, the ^{1}H-NMR spectrum can provide valuable information as shown in Figure 27.

Table 26: Results of the scope of the Suzuki-Miyaura reaction at a reaction time of 1 hour.

Entry[a]	-R	*E*/*Z*-12[b]	*Z*/*E*-13[b]	Conv. (%)[c]
b	-*p*-H	47/53	64/36	73
c	-*p*-OCH_3	48/52	79/21	47

a) All the reactions were performed under inert atmosphere. b) The *E*/*Z*-ratio was determined from ^{1}H-NMR spectroscopy, thanks to characteristic doublets of the vinylic proton around 6 ppm. c) Conversion was obtained by comparing the doublets of the starting material with the doublets of the products in the ^{1}H-NMR spectrum.

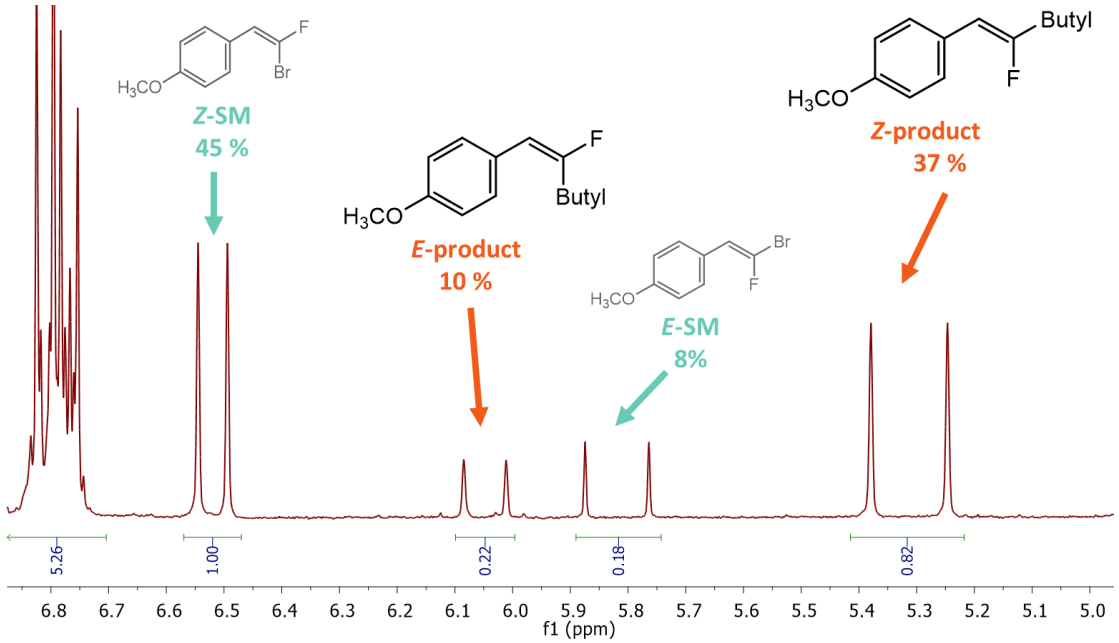


Figure 27: ^{1}H-NMR spectrum of partially synthesized (2-butyl-2-fluorovinyl)-4-methoxybenzene through Suzuki-Miyaura reaction after 1 hour reaction time and reaction circumstances as given in Reaction 13.

The ^{1}H-NMR spectrum (Figure 27) of (2-butyl-2-fluorovinyl)-4-methoxybenzene shows four characteristic doublets of the vinylic protons that are located between 5.2 and 6.6 ppm. This is the area before the aromatic region.

Each doublet is caused by a spin-spin coupling of the fluorine atom with the hydrogen atom around the carbon-carbon double bond. Since each isomer of the starting material and the product has the fluorine and the hydrogen atom, they all have a doublet. Because the orientation of the compound or the surrounding atoms vary in each of these isomers (shielding), the doublets don't overlap and become characteristic for each form. The doublets can be differentiated by looking at the J-coupling of the fluorine atom and the hydrogen atom. Since J_{cis} is smaller than J_{trans}, *Z*-SM and *E*-product have a smaller distance between the peaks of their doublets than *E*-SM and *Z*-product.

The ^{1}H-NMR spectrum shows a large doublet for the *Z*-isomer of the starting material (45 %), but a small doublet for the *E*-isomer of the starting material (8 %). For the product, the doublet of the *E*-isomer is smaller (10 %), while the *Z*-isomer is more present (37 %). This confirms the statement that the *Z*-isomer of the starting material will turn into the *E*-isomer of the product and vice versa as explained in paragraph 1.4.

More importantly, the *E*-isomer of the starting material will react faster than the *Z*-isomer of the starting material. In other words, the *Z*-isomer of the product will be created faster than the *E*-isomer of the product.

This suggest that there is a certain time where the *Z*-isomer of the product is totally formed, but not the *E*-isomer. That there is nearly no E-isomer formed after 1 hour is clearly seen in table 29 for the Suzuki-Miyaura reaction to create (2-butyl-2-fluorovinyl)benzene. This is also confirmed by the NMR spectrum (Figure 28).

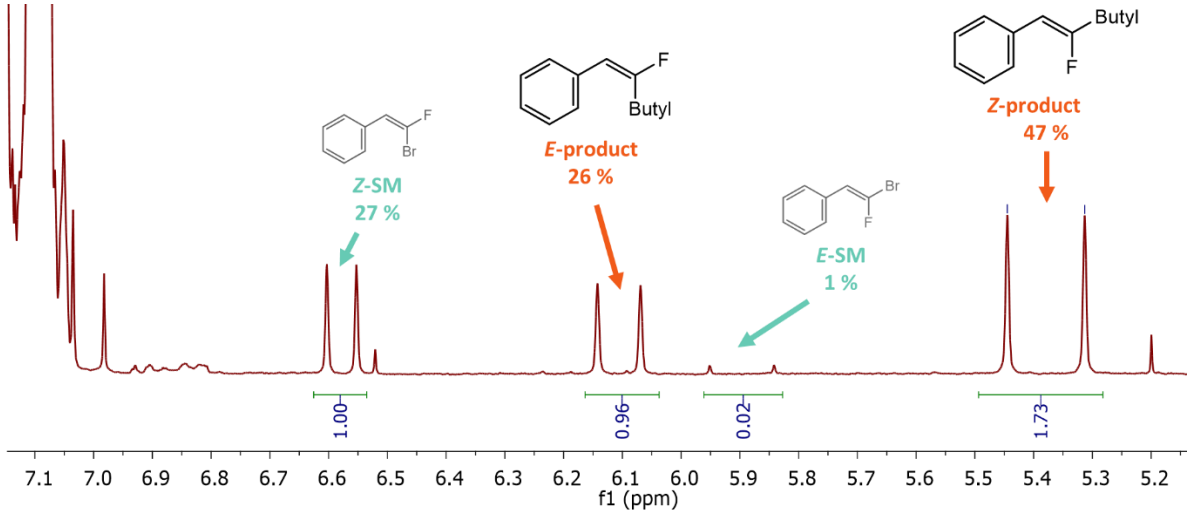


Figure 28: ^{1}H-NMR spectrum of partially synthesized (2-butyl-2-fluorovinyl)benzene through Suzuki-Miyaura reaction after 1 hour reaction time and reaction circumstances as given in Reaction 13.

This partially completed reaction, could be interesting because the remaining starting material can be separated more easily from the product. This way, a product that is enriched with the *Z*-isomer could be synthesized. However, this reaction time is very specific for each combination of substituent of the aromatic system, catalyst and base. Because there is still a numerous amount of *E*-isomer present in the product, this option was not further investigated in this research.

5.4.2 Three hours reaction time

The reaction time was fixed at three hours. The synthesis of (2-butyl-2-fluorovinyl)-4-methoxybenzene (Reaction 13) was finished after three hours, but for the products with different substituents on the aromatic compound this was not always the case (Table 27). When the reaction was not completed, no purification of the product was done. However, these syntheses can provide information of the reactivity of the products.

The highest conversion-ratio is achieved with entry **a**, **c** and **f** (Table 27), followed by entry **b**, **g** and **h**. There is no general trend, these results suggest that the electronic effect is not the most important property that influences the reaction rate. Furthermore, the para-substituents -OCH_3 and -NO_2 seem to react faster than the ortho-substituent -OCH_3 and meta-substituent -NO_2.

Table 27: Results of the scope of the Suzuki-Miyaura reaction after a reaction time of 3 hours.

Entry[a]	-R	*E*/*Z*-12[b]	*Z*/*E*-13[b]	Conv. (%)[c]
a	-*p*-NO_2	46/54	51/49	100[d]
b	-*p*-H	47/53	47/53	95
c	-*p*-OCH_3	48/52	40/60	100
d	-*p*-CF_3	50/50	60/40	80
e	-*p*-CO_2CH_3	45/45	57/43	66
f	-*p*-F	48/52	48/52	100
g	-*p*-Cl	47/53	53/47	87
h	-*p*-CH_3	49/51	55/45	87
i	-*o*-OCH_3	41/59	52/48	75
j	-*m*-NO_2	53/48	57/43	78

a) All the reactions were performed under inert atmosphere. b) The *E*/*Z*-ratio was determined from ^{1}H-NMR spectroscopy, thanks to characteristic doublets of the vinylic proton around 6 ppm. c) Conversion was obtained by comparing the doublets of the starting material with the doublets of the products in the ^{1}H-NMR spectrum. d) Results obtained through previous research [17].

Knowing that the reaction was not complete at three hours, it could be useful to look at the amount of isomer that remained at this time. By integrating the characteristic doublets in the ^{1}H-NMR spectrum, a percentage of isomers can be calculated as shown in Figure 27 and Figure 28.

The results of this integration are shown in Table 28 and the same conclusion as in paragraph 5.4.1 can be drawn from these results. The *Z*-isomer of the product will be created faster than the *E*-isomer of the product. After three hours reaction time, the *E*-isomer was fully converted in most cases, while significant amounts of *Z*-isomers of the SM were present.

The reactivity of the *E* and *Z* isomers vary when other substituents are used in the cross-coupling. The greatest difference in reactivity between the two isomers is seen with the -*o*-OCH_3 substituent. After three hours of reaction time, 25 % of the *Z*-isomer of the SM remained while the *E*-isomer was completely converted. The -*p*-CO_2CH_3 substituted product shows less difference in reactivity.

Table 28: Results of the scope of the Suzuki-Miyaura reaction after a reaction time of 3 hours, divided in the percentage occurrence of the isomers of the starting material and of the product.

Entry[a]	-R	Starting Material (12)		Product (13)		conv. (%)[c]
		% *E*-isomer[b]	% *Z*-isomer[b]	% *Z*-isomer[b]	% *E*-isomer[b]	
a	-*p*-NO_2	0	0	51[d]	49[d]	100[d]
b	-*p*-H	0	5	45	50	95
c	-*p*-OCH_3	0	0	49	51	100
d	-*p*-CF_3	7	14	48	32	80
e	-*p*-CO_2CH_3	11	23	38	28	66
f	-*p*-F	0	0	48	52	100
g	-*p*-Cl	0	13	47	41	87
h	-*p*-CH_3	0	13	48	39	87
i	-*o*-OCH_3	0	25	39	36	75
j	-*m*-NO_2	8	14	45	33	78

a) All the reactions were performed under inert atmosphere. b) The % of the isomers were determined from ^{1}H-NMR spectroscopy, thanks to characteristic doublets of the vinylic proton around 6 ppm. c) Conversion was obtained by comparing the doublets of the starting material with the doublets of the products in the ^{1}H-NMR spectrum. d) Results obtained through previous research [17].

5.4.3 Six hours reaction time

To obtain the best isolated yields (by column chromatography), the reaction time was increased to six hours. This reaction time was arbitrary chosen to be sure that all products are completely converted, although some substitutes require less time for completion.

Table 29 gives the results after reaction time of six hours. The isolated yields vary between 81 and 99 %. No relation between the electronic effects of the substituents and the yield was observed.

There is almost no change between the *E*/*Z*-ratio of the starting materials and the *Z*/*E*-ratio of the product except for the -*p*-NO_2 substituent and the -*p*-OCH_3 substituent where there is a change of 9% and 7% respectively. This means that the Suzuki-Miyaura reaction is mostly valid for both of the isomers.

Table 29: Results of the scope of the Suzuki-Miyaura reaction after a reaction time of 6 hours.

Entry[a]	-R	*E*/*Z*-12[b]	*Z*/*E*-13[b]	Yield (%)[c]
a	-*p*-NO_2	46/54	48/52	99
b	-*p*-H	47/53	46/54	81
c	-*p*-OCH_3	48/52	41/59	96
d	-*p*-CF_3	50/50	53/47	95
e	-*p*-CO_2CH_3	45/55	46/54	89
g	-*p*-Cl	47/53	46/54	88
h	-*p*-CH_3	49/51	49/51	96
i	-*o*-OCH_3	41/59	40/60	81
j	-*m*-NO_2	53/48	49/51	99

a) All the reactions were performed under inert atmosphere. b) The *E*/*Z*-ratio was determined from ^{1}H-NMR spectroscopy, thanks to characteristic doublets of the vinylic proton around 6 ppm. c) Isolated yields were obtained after purification of the product by column chromatography on silica gel.

6 CONCLUSION AND RECOMMENDATION

The starting material was synthesized with *E*/*Z*-ratio's around 50/50 through a Wittig reaction with the corresponding aldehyde. A partial separation of the *E*- and *Z*-isomers could be achieved by washing the solid product with small quantities of petroleum ether.

Concerning the isomerization, photosensitizers Benzil and 9-fluorenone has shown promising results towards the *E*-isomer under irradiation at 365 nm. For Benzil, the best conditions gave an interesting *E*/*Z*-ratio of 81/19. With 9-fluorenone a product with an *E*/*Z*-ratio of 90/10 could even be obtained. Photosensitizer Acetophenone has shown one good result towards the *Z*-isomer. However, this result could not be confirmed. Further experiments are necessary to solve the reproducibility issues for most photosensitizers and improve the E/Z ratio.

Each photosensitizer has an optimal reaction time, higher reaction times do not seem to improve the ratio. Oxygen has an important impact on the isomerization and could induce degradation. Toluene, methanol and acetonitrile seem to be the best solvents to perform isomerization reactions with 9-fluorenone. The reaction in flow (with 9-fluorenone) showed low yields and very low isomerization.

The Suzuki-Miyaura reaction was optimized for the formation of alkylfluorostilbenes. Catalyst Pd_2dba_3/Xantphos showed the best results towards the conversion rate and the stereoselectivity. From the tested temperatures, 80°C gave the best results for the Suzuki-Miyaura reaction. Furthermore, ^{1}H-NMR spectra analysis of the crude mixture showed that the *E*-isomer of the starting material reacts faster than the *Z*-isomer.

A scope of the Suzuki-Miyaura cross-coupling was performed by varying the substituents on the aromatic ring. These reactions yielded 81 to 99 % after purification by column chromatography. The reaction provided excellent stereoselectivity. Since the nine different substituents on the -ortho, -meta and -para position gave very good results, the Suzuki-Miyaura cross-coupling reaction has a wide range of applications.

Future research could be centred on the isomerization with 9-fluorenone or Benzil to obtain a robust protocol. The scope of the Suzuki-Miyaura reaction could be expanded for different alkyl boronic acids.

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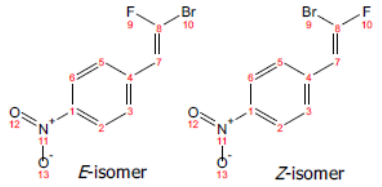
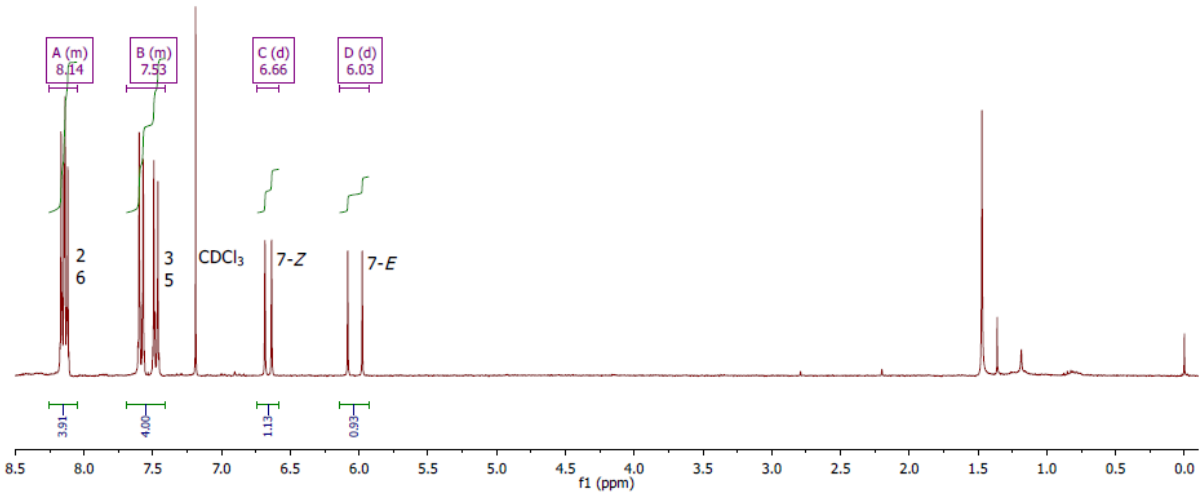
APPENDIX

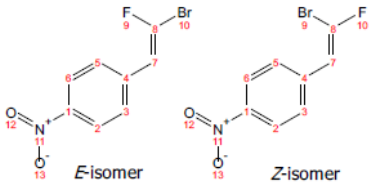
^{1}H-NMR of SM: (2-bromo-2-fluorovinyl)-4-nitro-benzene (product 12a)



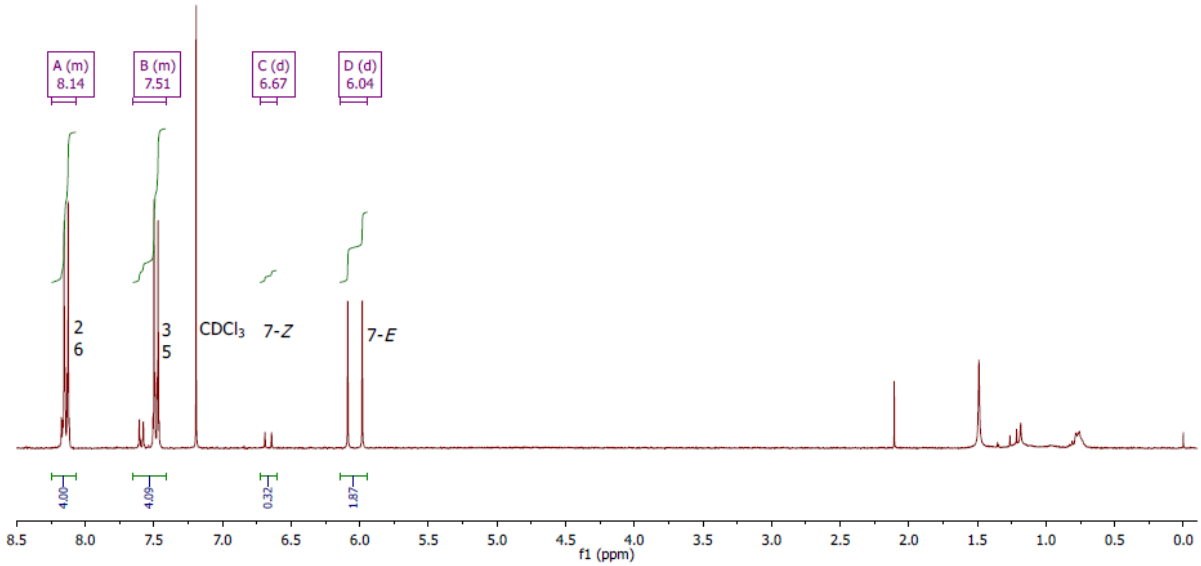
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.26 – 8.05 (m, 4H), 7.69 – 7.41 (m, 4H), 6.66 (d, J = 14.4 Hz, 1H), 6.03 (d, J = 31.7 Hz, 1H).



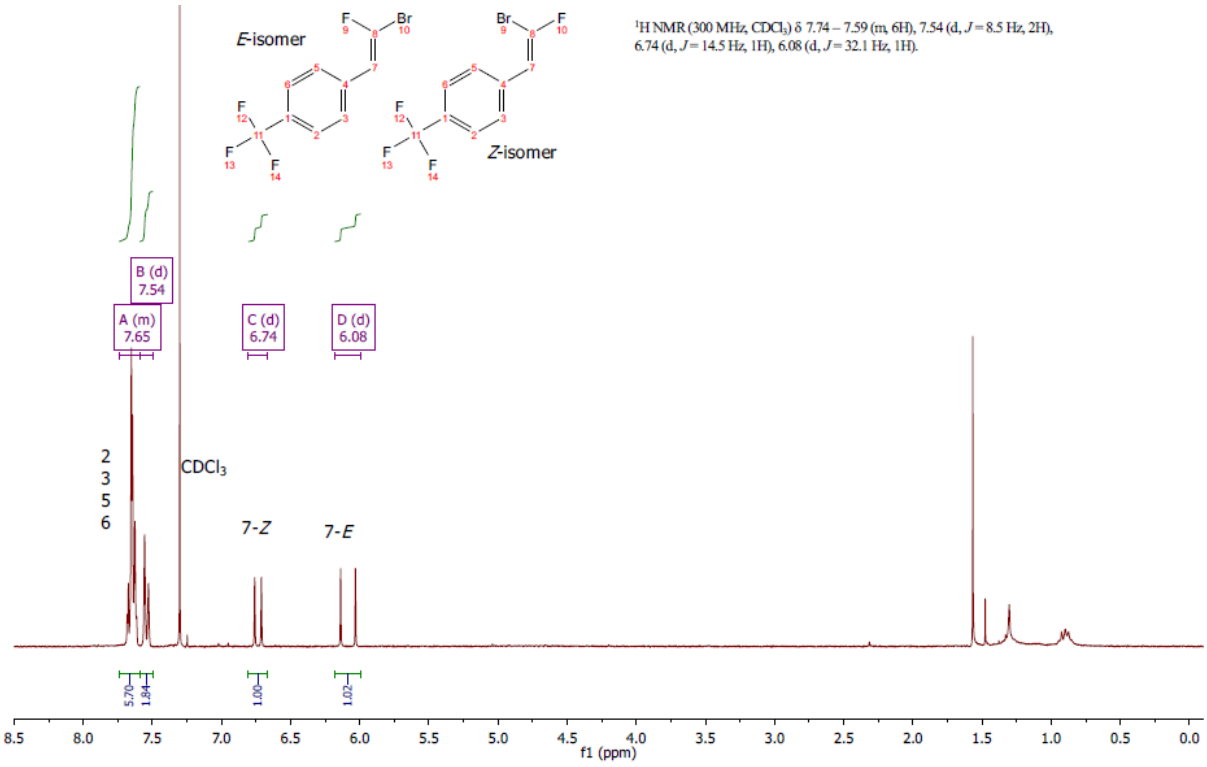
^{1}H-NMR of SM: (2-bromo-2-fluorovinyl)-4-nitro-benzene (product 12a) enriched by the *E*-isomer



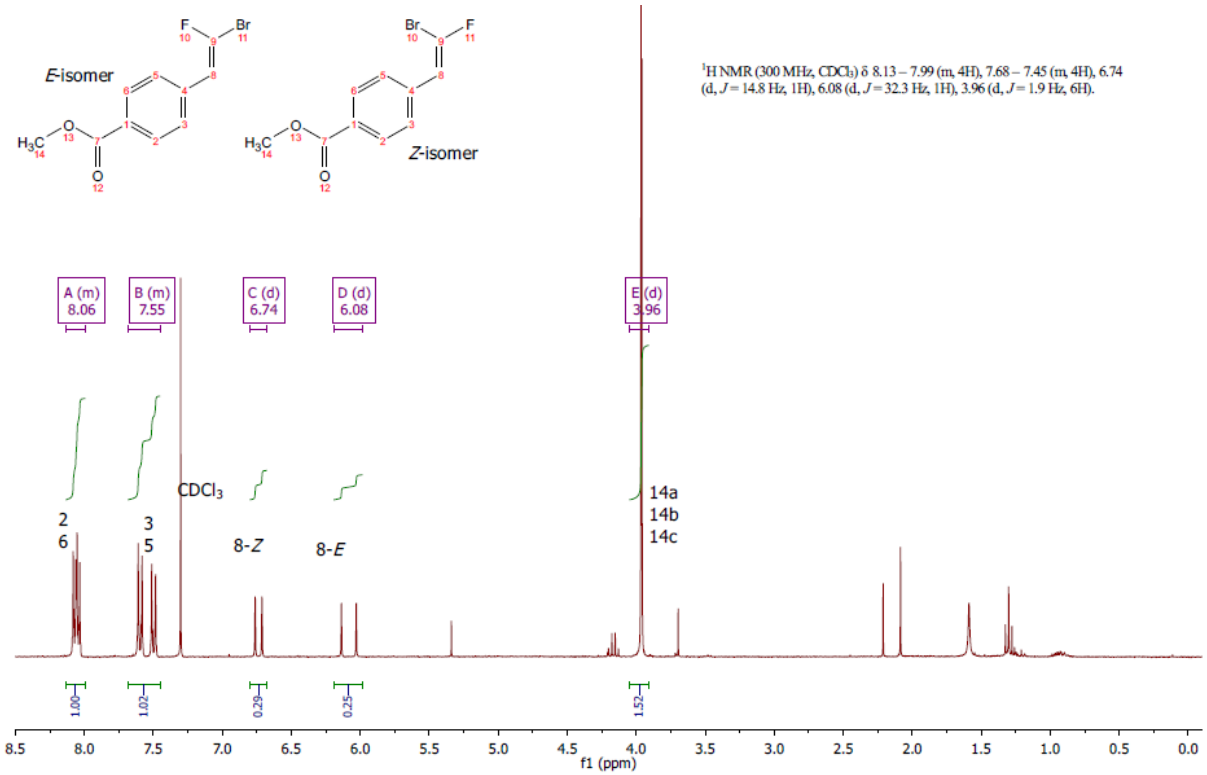
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.25 – 8.07 (m, 4H), 7.65 – 7.41 (m, 4H), 6.67 (d, J = 14.4 Hz, 1H), 6.04 (d, J = 31.7 Hz, 1H).



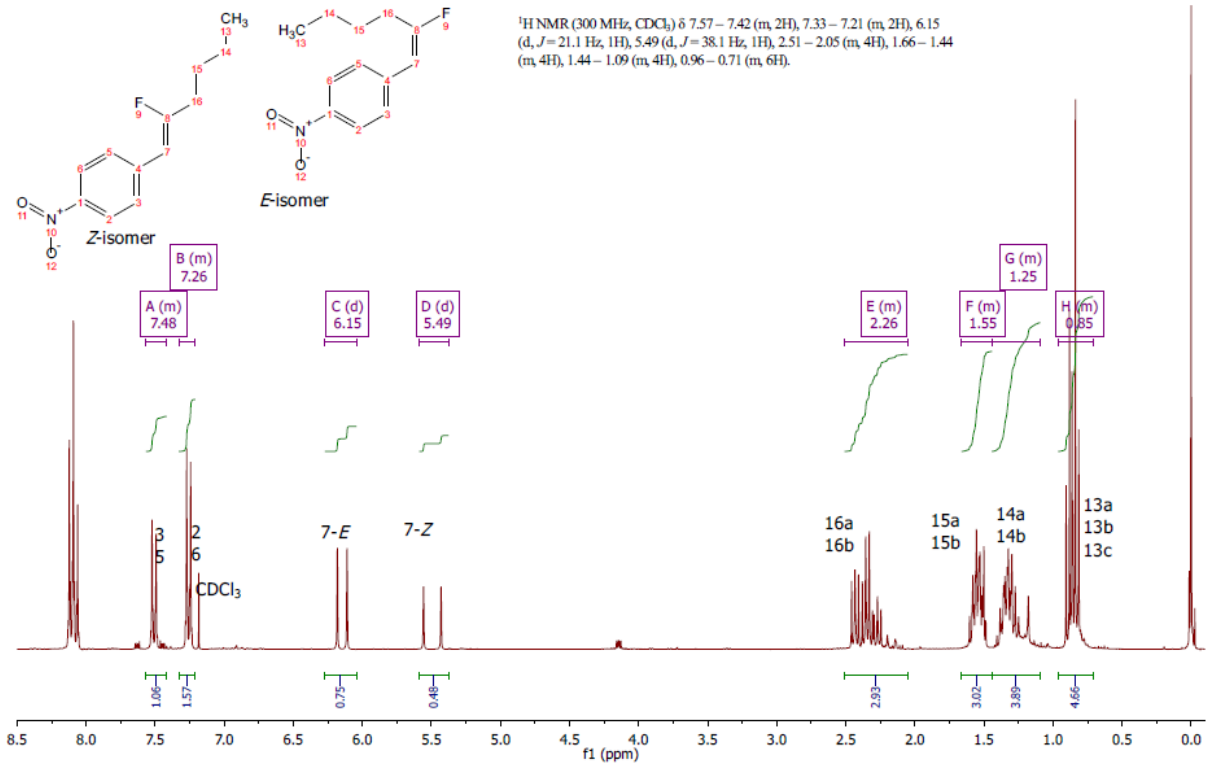
[1]H-NMR of SM: (2-bromo-2-fluorovinyl)-4-(trifluoromethyl)-benzene (product 12b)



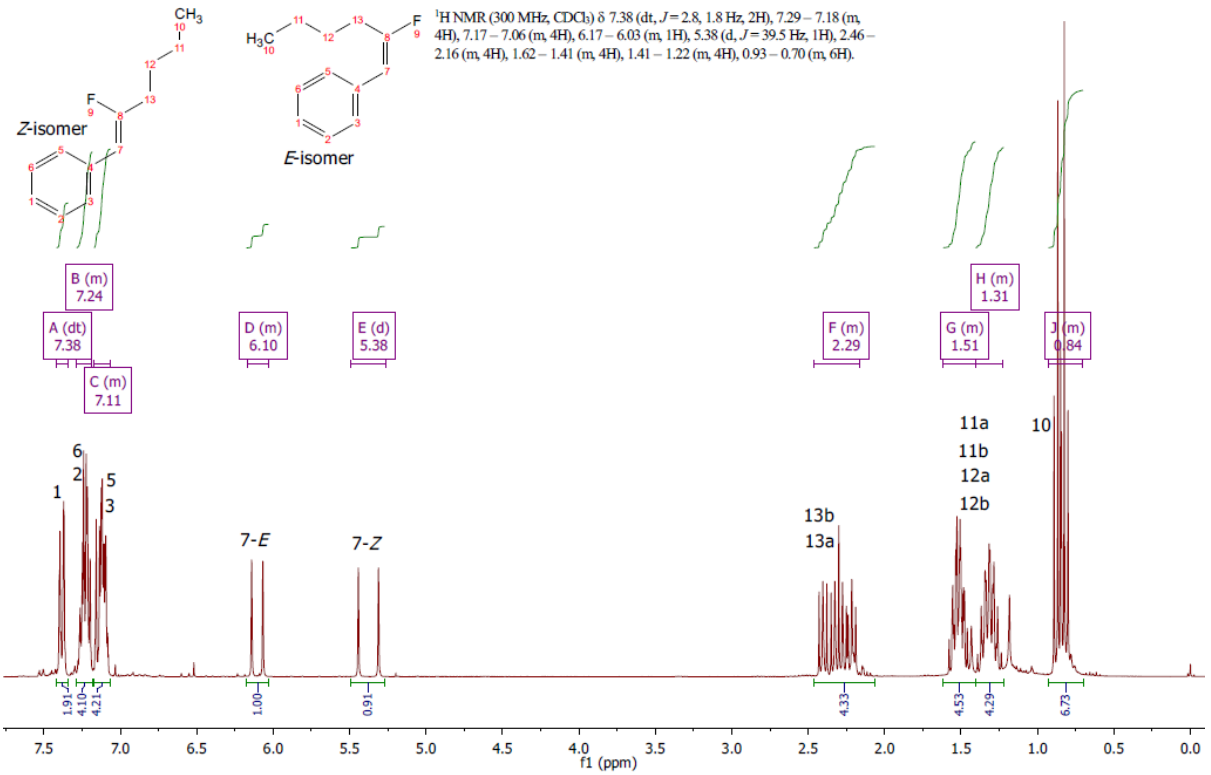
[1]H-NMR of SM: methyl 4-(2-bromo-2-fluorovinyl)benzoate (product 12c)



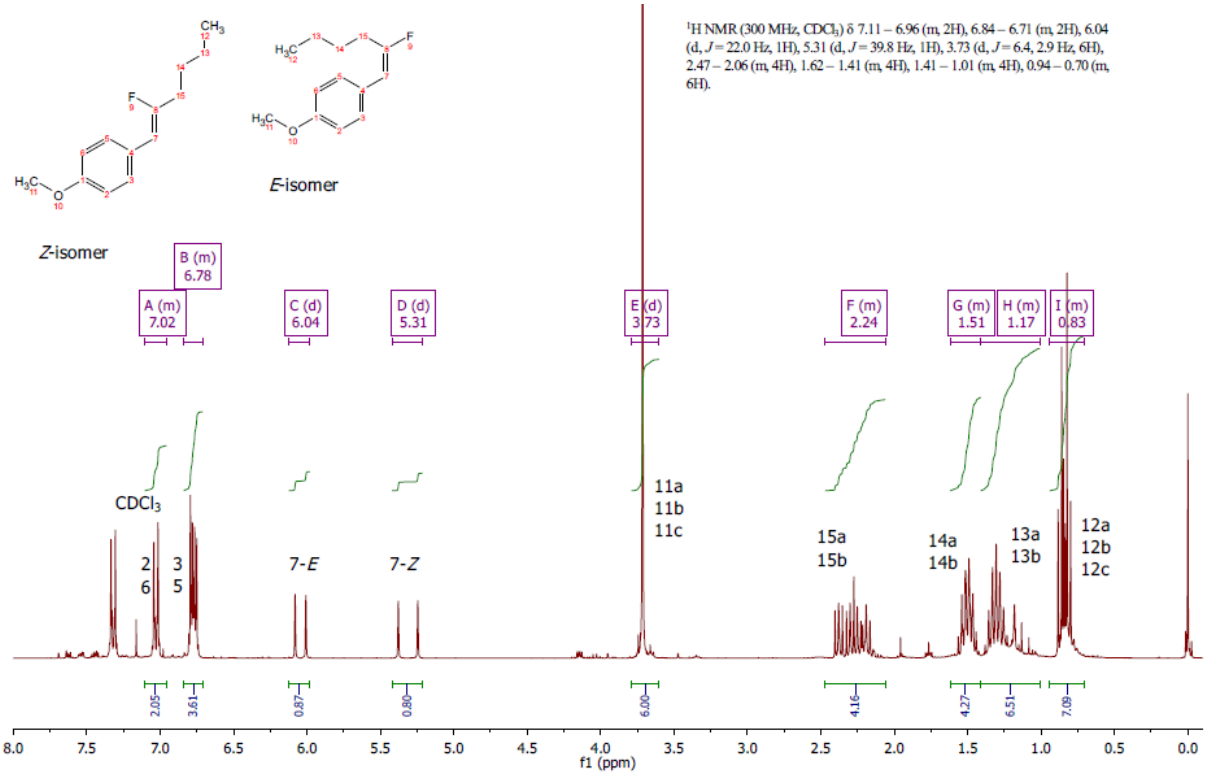
[1]H-NMR of (2-butyl-2-fluorovinyl)-4-nitro-benzene (product 13a) at six hours reaction time



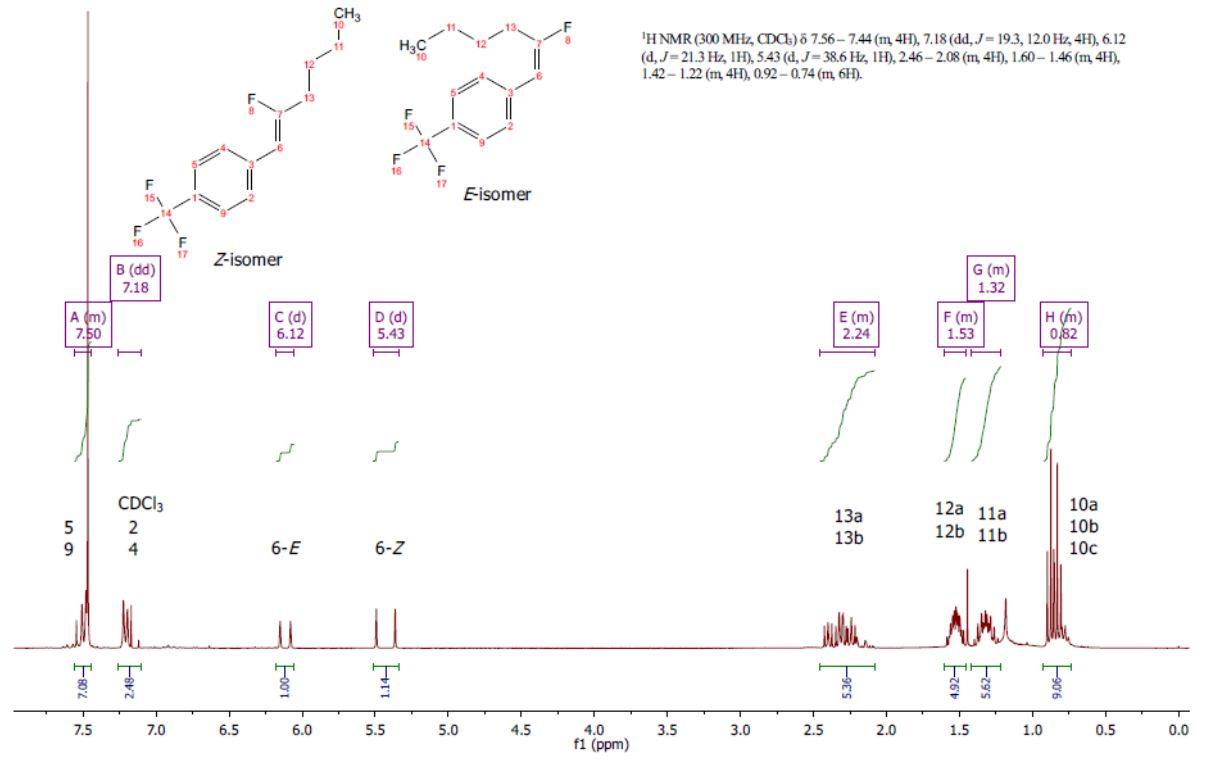
[1]H-NMR of (2-butyl-2-fluorovinyl)benzene (product 13b) at six hours reaction time



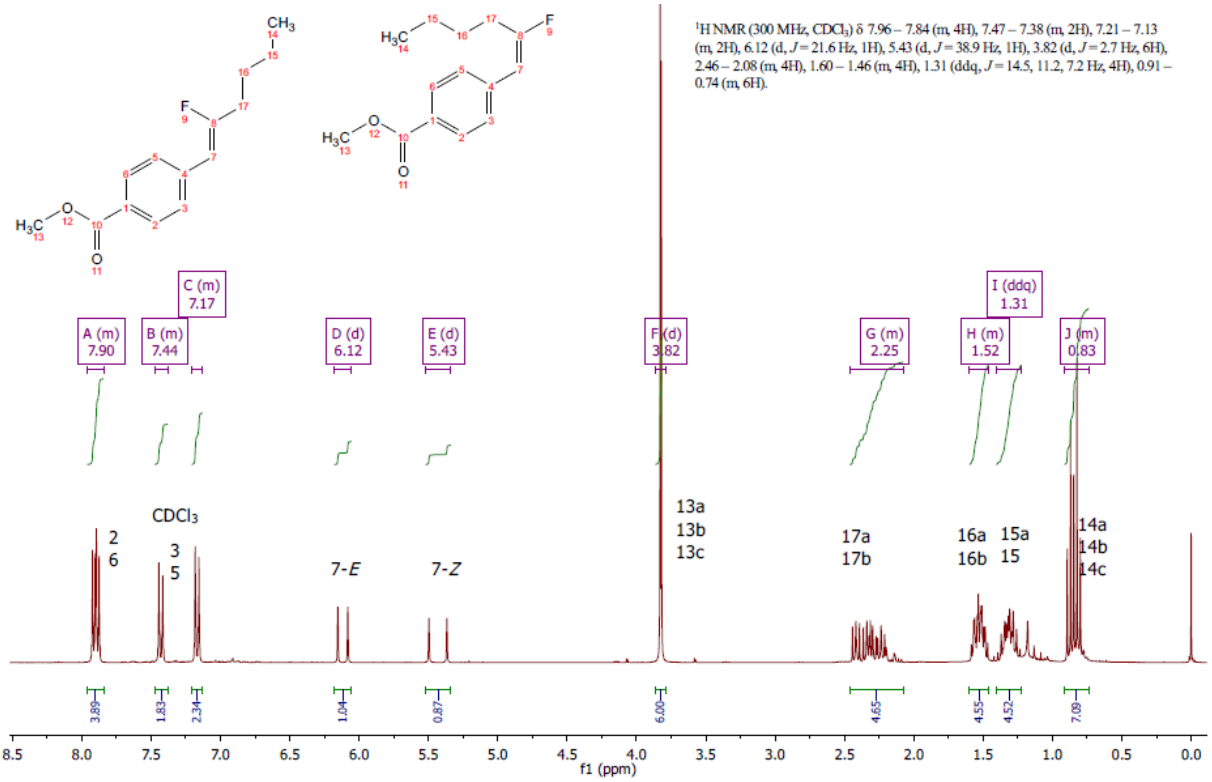
[1]H-NMR of (2-butyl-2-fluorovinyl)-4-methoxybenzene (product 13c) at six hours reaction time



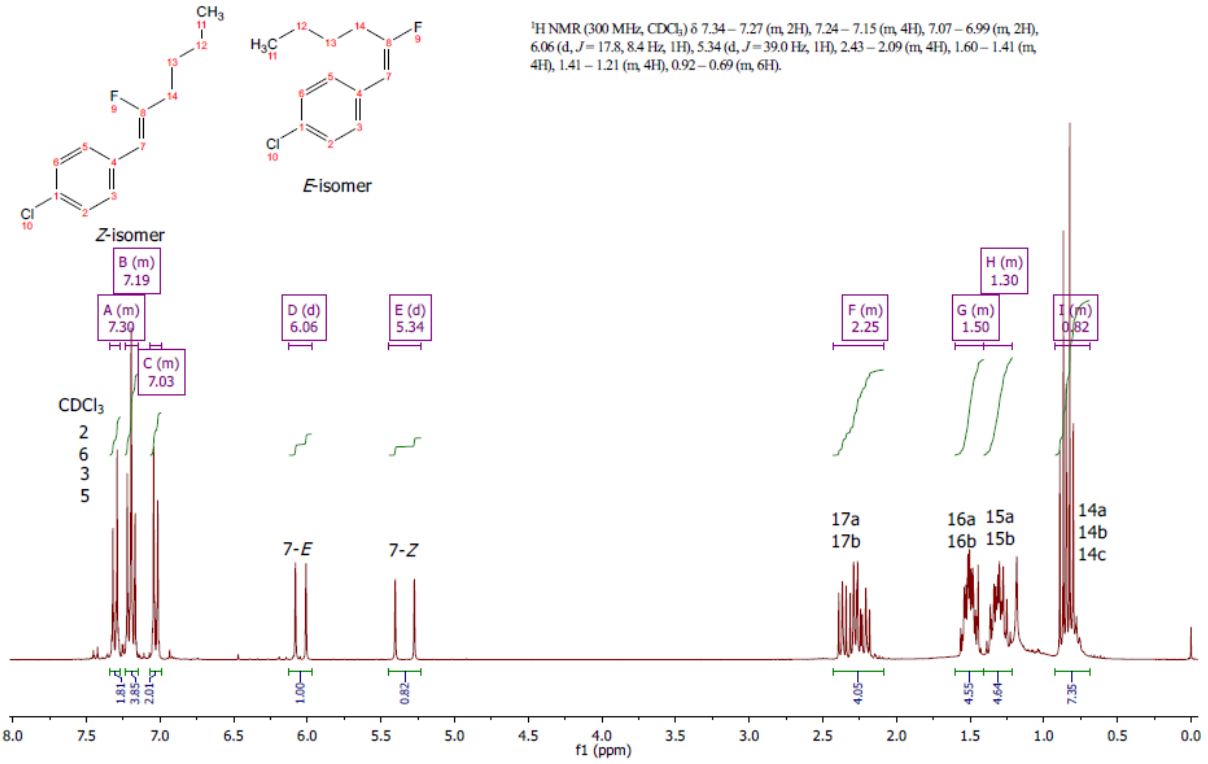
[1]H-NMR of (2-butyl-2-fluorovinyl)-4-trifluoromethyl-benzene (product 13d) at six hours reaction time



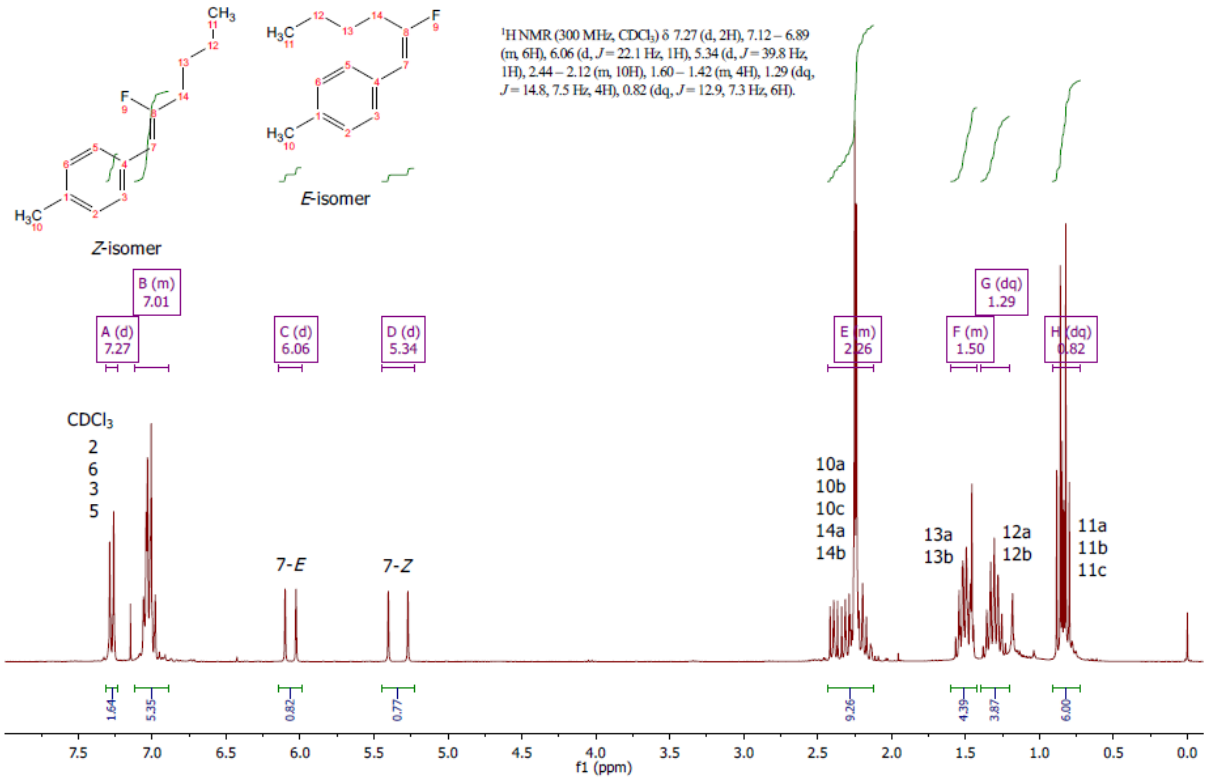
[1]H-NMR of methyl-4-(2-fluorohex-1-en-1-yl)benzoate (product 13e) at six hours reaction time



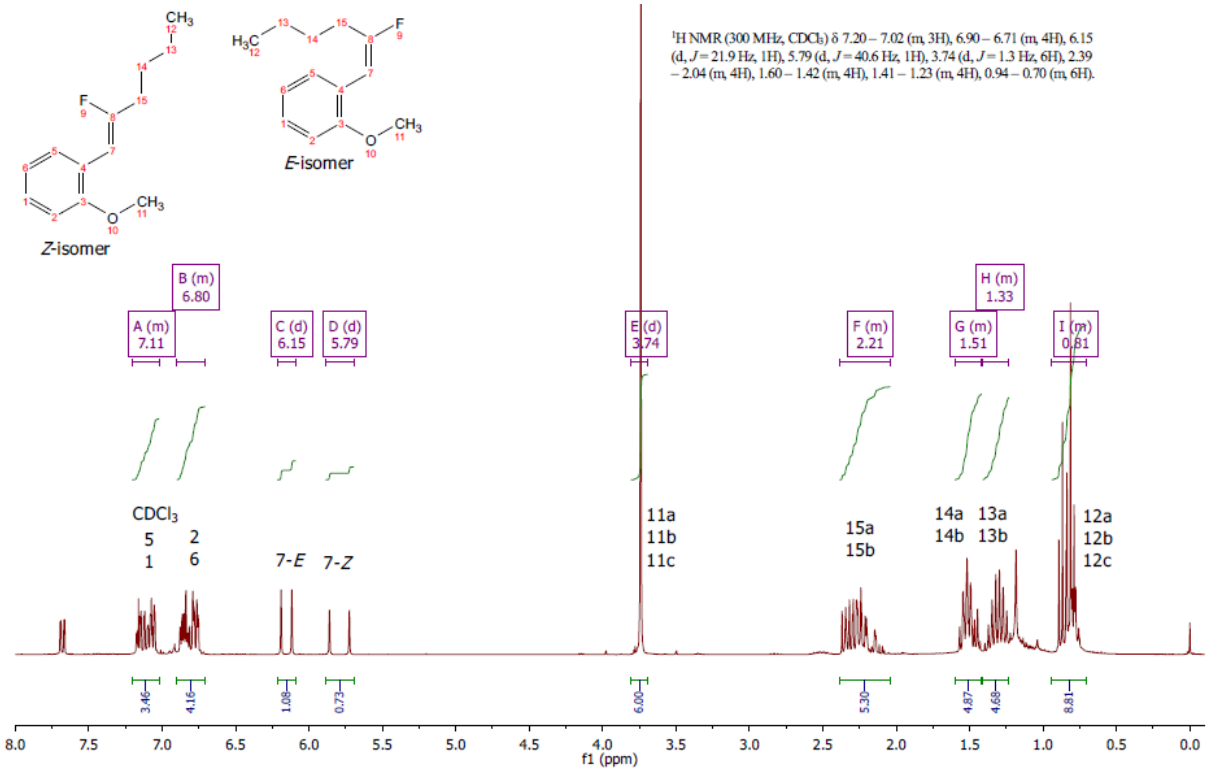
[1]H-NMR of (2-butyl-2-fluorovinyl)-4-chloro-benzene (product 13g) at six hours reaction time



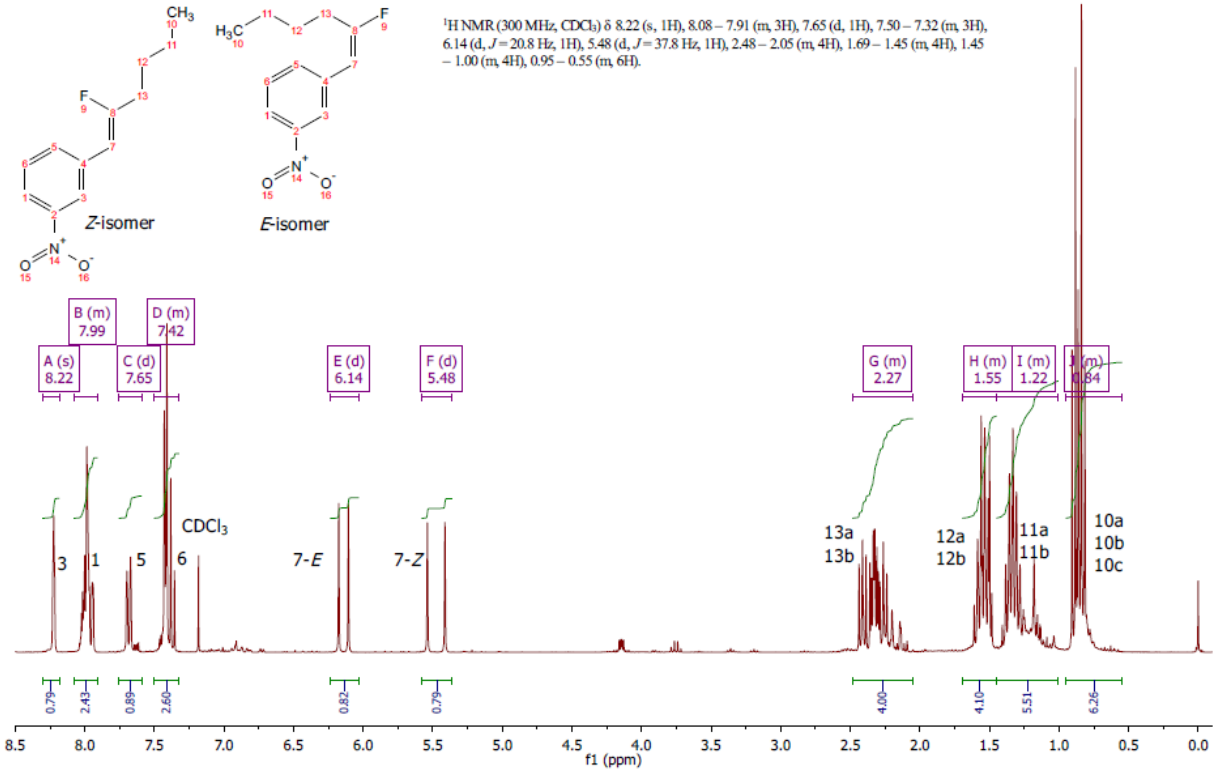
[1]H-NMR of (2-butyl-2-fluorovinyl)-4-methyl-benzene (product 13h) at six hours reaction time



[1]H-NMR of (2-butyl-2-fluorovinyl)-2-methoxybenzene (product 13i) at six hours reaction time



^{1}H-NMR of (2-butyl-2-fluorovinyl)-3-nitrobenzene (product 13j) at six hours reaction time



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Development of the first Suzuki-Miyaura cross-coupling for the formation of alkylfluorostilbenes and studies of the E/Z- isomerization of (2-bromo-2-fluorovinyl)benzene derivatives

Richting: **master in de industriële wetenschappen: chemie**
Jaar: **2016**

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Datum: **13/06/2016**